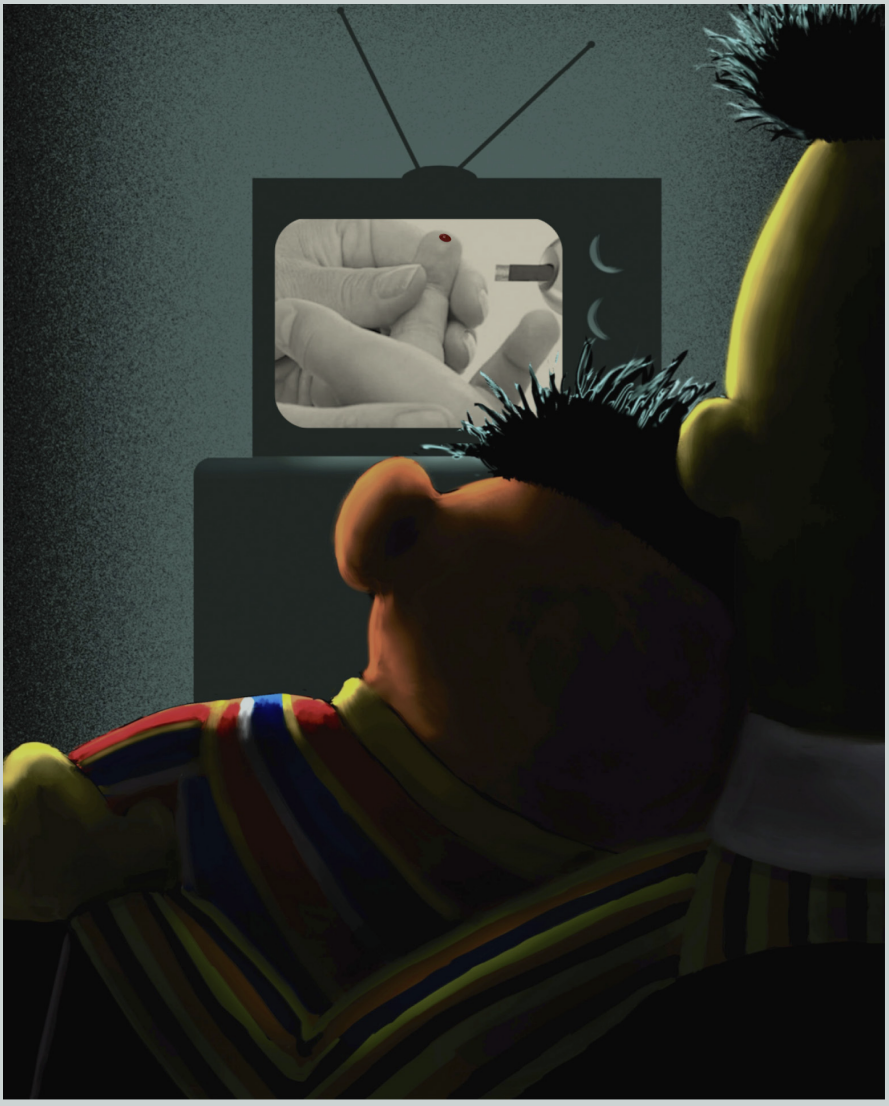
SERIOUS INFECTION IN ACUTELY ILL CHILDREN IN PRIMARY CARE

Validating clinical prediction rules and the added value of vital signs and point-of-care tests.



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May 2015

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SERIOUS INFECTION IN ACUTELY ILL CHILDREN IN PRIMARY CARE

VALIDATING CLINICAL PREDICTION RULES AND THE ADDED VALUE OF VITAL SIGNS AND POINT-OF-CARE TESTS

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Dissertation presented in partial fulfilment of the requirements for the degree of Doctor in Biomedical Sciences

May 2015

Cover: adaptation of: The New Yorker, June 2013.

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INTRODUCTION

Acute infection is one of the most common problems of children attending primary care and represents an important proportion of a general practitioner's workload.[3] Febrile illness accounts for 20% of all visits to the paediatric emergency department.[4]

In contrast, serious infections are rare in children in developed countries, but associated with considerable morbidity and mortality.[5] In a primary care setting, less than 1% of children will have a serious infection.[1, 6] The incidence of serious infections in children is assumed to be 5 to 10 times higher at the paediatric emergency department, as seen in one of our recent studies.[6] In Flanders, infectious diseases are responsible for 13.8% of all deaths in children under the age of one year, and for 4.6% of deaths in children aged 1 to 14 years,[7] comparable to death rates previously reported in the UK.[8]

Serious infections in children are usually defined as sepsis (including bacteraemia), meningitis, pneumonia, complicated urinary tract infection, bacterial gastroenteritis with dehydration, osteomyelitis, and cellulitis.[5] Their consequences can be severe; the mortality of meningococcal disease can be as high as 14%,[9-12] and approximately 7% of children who survive bacterial meningitis suffer from hearing loss.[13]

These serious infections need to be distinguished from the vast majority of non-serious infections in children, which can be challenging especially in primary care. Those few children with a serious infection can present at an early stage when the severity of the infection is not yet apparent.[5] At that point, their symptoms tend to mimic those of children with a non-serious viral infection. This could cause a diagnosis to be missed at first contact, sometimes with serious consequences, due to the rapid deterioration of the illness.

Clinical prediction rules and guidelines may assist in the early recognition of serious infections, especially in low prevalence settings where a high sensitivity is essential to effectively rule out serious infection.[5] Clinical prediction rules can be constructed to achieve maximum sensitivity (in contrast to red flags that can rule in serious infection). There is a widely accepted methodology for the development of clinical prediction rules.[14-16]
The derivation of a clinical prediction rule is the first of three steps required before it can be disseminated and used in practice. This is followed by internal and external validation before finally testing the impact of its use on clinical outcomes.[2] (**Figure I**)
These steps require cumulative levels of evidence and the adoption of several types of study designs to answer the relevant research and clinical questions.

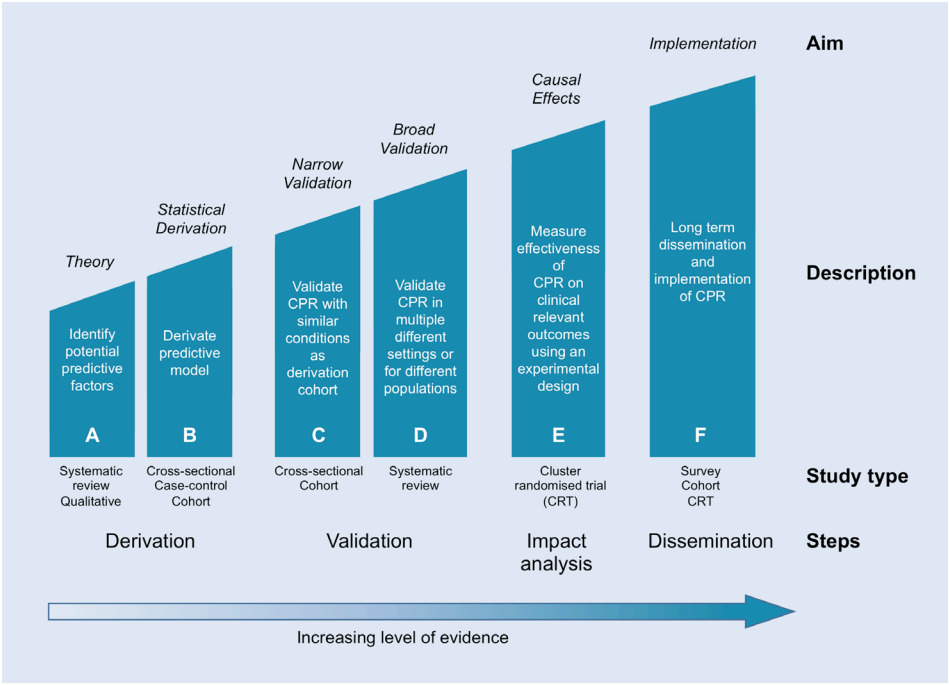

Figure I: Framework for study designs from theory to implementation of clinical prediction rules[2]

The increasing number of clinical prediction rules reported in the literature have a tendency to focus on the derivation stage with only a minority progressing to validation and very few undergoing impact analysis.[17, 18]
This framework should be considered as a cyclical rather than linear process, allowing you to retrace your steps and add new predictors to the model to increase diagnostic performance (e.g. adding C-reactive protein test results if external validation (**Chapter 1 & 3)** demonstrates low positive predictive value). (**Figure I, Step B; Chapter 5**)

Over the last decade our research team has studied the value of clinical signs for the diagnosis of serious infections in acutely ill children in primary care,[1, 19] resulting in a systematic review of clinical features to identify serious infection in children in developed countries.[5] (**Figure I, Step A**)
Our research group conducted the largest study on the diagnosis of serious infections in children in primary care so far, in which over 4000 children were included prospectively to construct a decision tree based on signs and symptoms.[1] (**Figure I, Step B**) The decision tree had a sensitivity of nearly 100%. The probability, however, of having a serious infection in children testing positive, was approximately 6%. (**Figure II**)

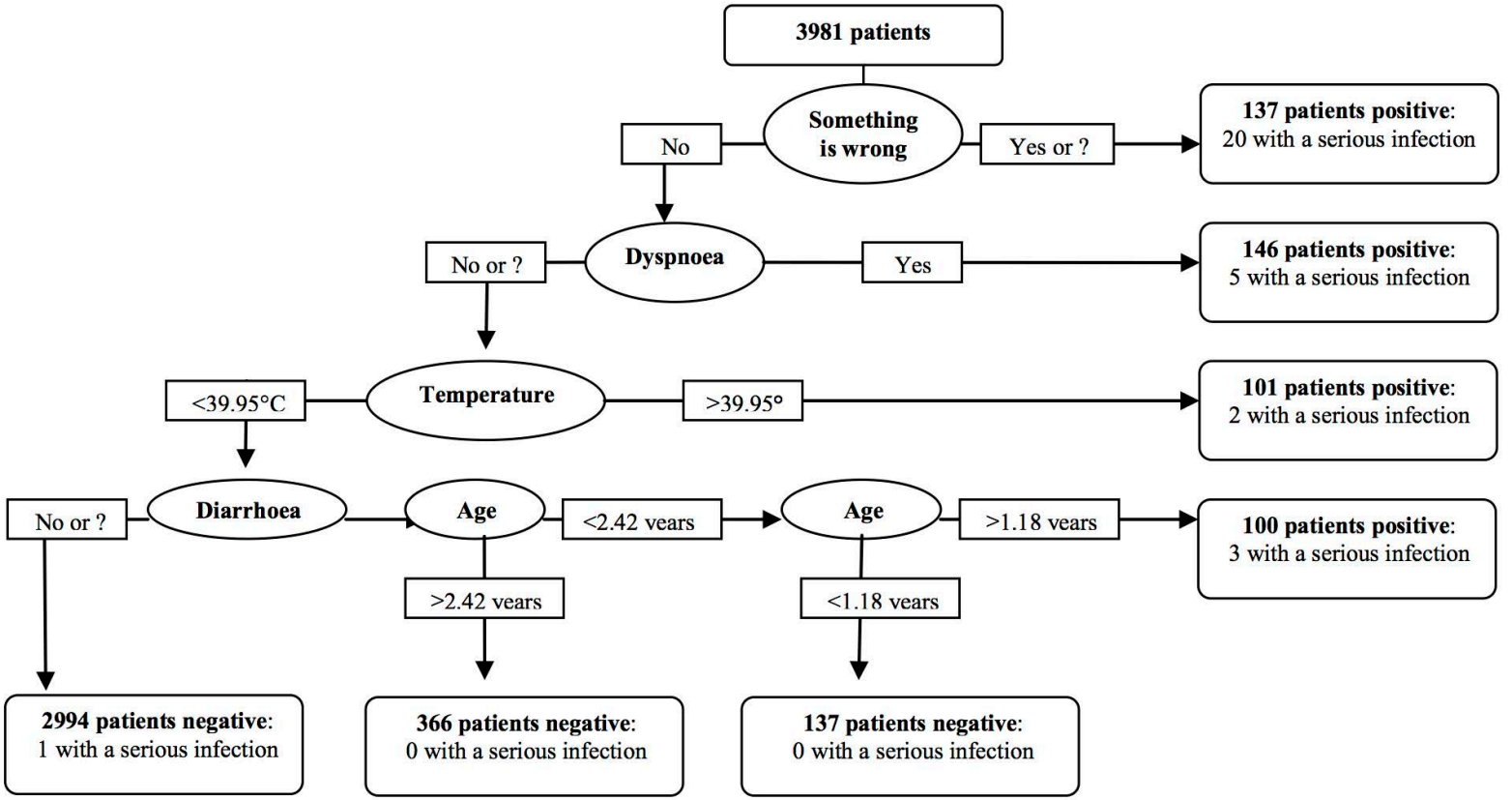

Figure II: Decision tree for any serious infection in children (prior probability = 0.78% across all settings with 31 serious infections)[1]

This decision tree was identified by a systematic review as the only one developed in primary care, demonstrating best performance at ruling out for the composite outcome of serious infections.[5] It is easy to interpret as compared to other multivariable models, such as logistic regression-based models, making it more practical in a clinical setting.[1]
In this thesis, I aim to validate this decision tree in a new population (**Figure I, Step C & D**) and explore the added value of technological tests, such as point-of-care (POC) tests in diagnosing serious infection in acutely ill children in primary care. (**Figure I, Step B & D**)

POC tests are defined as laboratory and other services provided to patients at the bedside. The physician has an immediate result and management can be adjusted accordingly. This makes them especially attractive in situations where a fast decision is warranted, such as urgent-access primary care. They are minimally invasive, and thus relevant in paediatric care.

Members of our research team performed a systematic review of the literature in all relevant databases to identify the laboratory tests used to detect serious infections in febrile children in ambulatory care settings.[20]

The most probable candidates for this purpose are C-reactive protein (CRP) and procalcitonin (PCT). CRP has been shown to decrease antibiotic prescriptions and predict bacterial aetiology of community-acquired pneumonia.[21, 22] PCT has been shown to correlate with severity of urinary tract infections and sepsis and of community acquired pneumonia in children.[23, 24]
Despite these promising results, evidence is not yet conclusive because most studies were performed in secondary care settings and other tests may be valuable as well. In addition, their use was limited because they required a normal blood sample to be sent off to the laboratory and results would become available too late to influence clinical management.
At present, there is only one POC test for procalcitonin, which takes 30 minutes to produce a result and requires blood centrifugation, making it unsuitable for use in acute ambulatory care, especially in general practice where consultations last between 10-15 minutes. On the other hand, a fast and accurate POC test for CRP is available that produces a result within 4 minutes.

If the decision tree proves to be useful after external validation (retro- and prospectively), a point-of-care CRP test might be able to increase the diagnostic accuracy by reducing the number of children testing false positive on this decision tree.

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OBJECTIVES

The **research question** of this thesis can be formulated as follows:
"In addition to measuring clinical signs and symptoms, can new or existing technology improve the early identification of seriously ill children in primary care?" More specifically, after applying the decision tree, can I further reduce the number of false positives (and thus increase the specificity) and maintain the same level of sensitivity?

To study this research question, I aim to:
- identify and validate the clinical features used for diagnosing serious infections in acutely ill children (Part 1)
- determine the analytical and diagnostic accuracy, and the added value of a carefully selected point-of-care test (Part 2)

In **Chapter 1**, I focus on the clinical prediction rules based on vital signs and symptoms, recently identified by a systematic review for use in ambulatory care populations (**Figure I, Step A**) and attempt to validate these rules in seven urgent-access datasets shared as part of an international network, and compare these results to recent findings in other studies. (**Figure I, Step D**)

Clinical prediction rules tend to perform worse when validated in a new setting. I attempt to validate hospital-centred clinical prediction rules based on vital signs to detect serious infection in children admitted to an inpatient paediatric ward in **Chapter 2.** (**Figure I, Step D**)

Chapter 3 describes the results of a prospective temporal & geographic validation of the best-performing decision tree in **chapter 1 & 2** (in terms of ruling out value) based on signs and symptoms in a new but similar population in Flanders. (**Figure I, Step C & D**)

Chapter 4 sets the scene for a large prospective trial with a feasibility study on the use of the point-of-care test in the intended setting, namely ambulatory primary care. I examine the analytical accuracy and user-friendliness of a selected point-of-care test after careful selection of a device that meets all our preliminary requirements.

Chapter 5 describes the results of the prospective diagnostic accuracy study, aiming to explore the added value of the selected point-of-care test in primary care, updating the clinical prediction rule with a new test. (**Figure I, Step D**) I focus on the clinical utility of this point-of-care test in three different ambulatory care settings: general practice, outpatient paediatric clinic, and the emergency department.

The final **discussion** ties all the chapters together and discusses the findings of each chapter in relation to the incidence of serious infections, the development of clinical prediction rules, and the use of safety netting advice and offers a perspective for future developments in the field of point-of-care testing in serious infections in paediatric primary care.

A PhD student from UGent, Marieke Lemiengre (Department of Family Practice and Primary Health Care, UGent) collaborates with this project. She examines the effect of the POC CRP test, a minimal intervention or both in comparison with usual care on antibiotic prescribing rate, the use of diagnostic tests and medical services, and parent's satisfaction.

PART 1: CLINICAL FEATURES

Aim

to identify vital signs and clinical prediction rules used for diagnosing serious infections in acutely ill children and assess their value in diagnostic triage.

Chapter 1.

Research question

How well do clinical prediction rules perform in identifying serious infections in acutely ill children across different ambulatory care settings?

Published as:

Jan Y Verbakel, Ann Van den Bruel, Matthew Thompson, Richard Stevens, Bert Aertgeerts, Rianne Oostenbrink, Henriette Moll, Marjolein Berger, Monica Lakhanpaul, David Mant, Frank Buntinx, for the European Research Network on Recognizing Serious Infection (ERNIE). How well do clinical prediction rules perform in identifying serious infections in acutely ill children across an international network of ambulatory care datasets? ***BMC Medicine 2013; 11:10.***

and:

Matthew Thompson, Ann Van den Bruel, Jan Y Verbakel, Monica Lakhanpaul, Tanja Haj-Hassan, Richard Stevens, Henriette Moll, Frank Buntinx, Marjolein Y Berger, Bert Aertgeerts, Rianne Oostenbrink, David Mant: Systematic review and validation of prediction rules for identifying children with serious infections in emergency departments and urgent-access primary care. ***Health Technol Assess 2012; 16:1 - 100.***

RETROSPECTIVE VALIDATION OF CLINICAL PREDICTION RULES FOR IDENTIFYING SERIOUS INFECTIONS IN ACUTELY ILL CHILDREN ACROSS AN INTERNATIONAL NETWORK OF AMBULATORY CARE DATASETS.

ABSTRACT

Background: Diagnosing serious infections in children is challenging because of the low incidence of such infections and their non-specific early presentation. Prediction rules are promoted as a means to improve recognition of serious infections. A recent systematic review identified seven clinical prediction rules, of which only one had been prospectively validated, calling into question their appropriateness for clinical practice. We aimed to examine the diagnostic accuracy of these rules in multiple ambulatory care populations in Europe.

Methods: Four clinical prediction rules and two national guidelines, based on signs and symptoms, were validated retrospectively in seven individual patient datasets from primary care and emergency departments, comprising 11023 children from the UK, the Netherlands, and Belgium. The accuracy of each rule was tested, with pre-test and post-test probabilities displayed using dumbbell plots, with serious infection settings stratified as low prevalence (LP; <5%), intermediate prevalence (IP; 5 to 20%), and high prevalence (HP; >20%). Sensitivity analyses of the selected clinical prediction rules were performed to avoid spectrum bias.

Results: In LP settings, the 4-step decision tree had highest sensitivity of 90% (95% CI 68-99%) at a specificity of 44% (95% CI 39-48%). The prediction rule with the second best sensitivity was the pneumonia rule, which had sensitivities above 92% for ruling out serious infections with specificities ranging from 41 to 45%. The UK NICE traffic light system and Dutch guideline achieved sensitivities between 81 and 100% and specificities between 1 and 85% in low or intermediate prevalence settings.

Conclusions: None of the clinical prediction rules examined in this study provided adequate diagnostic accuracy. In LP or IP settings, prediction rules and evidence-based guidelines had high sensitivity, providing promising rule-out value for serious infections in these datasets, although all had a percentage of residual uncertainty. Additional clinical assessment or testing such as point-of-care laboratory tests may be needed to increase clinical certainty. None of the prediction rules identified seemed to be valuable for HP settings such as emergency departments.

BACKGROUND

Acute infection is the most common presentation in children attending settings of ambulatory care (AC).[1, 2] Although most infections are self-limiting, they remain an important cause of morbidity and mortality in children in economically developed countries.[3-5] In the UK, infections account for 20% of childhood deaths, especially in children under 5 years of age.[6]
Serious infections in children are usually defined as sepsis (including bacteraemia), meningitis, pneumonia, bacterial gastro-enteritis with dehydration, osteomyelitis, cellulitis, and complicated urinary-tract infection (UTI; positive urine culture combined with systemic features such as fever).[3] As a result of immunization against Haemophilus influenzae and Streptococcus pneumoniae, the incidence of these diseases has decreased steadily over recent decades, and they are now estimated to account for less than 1% of all acute childhood infections in primary care (PC).[2, 7]

The combination of low incidence, non-specific initial clinical presentation, and potential for rapid deterioration makes the assessment of acutely ill children difficult.[8, 9] Clinical prediction rules and guidelines may assist in the early recognition of serious infections.[3] In a previous systematic review, we identified all available clinical prediction rules (seven in total), based on signs and symptoms, for identifying any serious infection (two rules), pneumonia (two), meningitis (two), and dehydration from bacterial gastroenteritis (one rule) in AC settings.[3] (**Table 1.1**)

a) Identified clinical prediction rules by systematic review:
1. Yale Observation Scale
2. 4-step Decision Tree
3. Pneumonia Rule I
4. Pneumonia Rule II
5. Meningitis Rule I
6. Meningitis Rule II
7. Gastro-enteritis Rule I

b) Identified clinical guidelines:
1. NICE Guideline on Feverish Illness in Children
2. Dutch College of General Practitioners Guideline

c) Identified clinical prediction rules by focused literature search:
1. Clinical Diagnostic Model for pneumonia, UTI, bacteraemia

Table 1.1: Identified clinical prediction rules and guidelines

Four of these seven clinical prediction rules were derived for use in emergency-care settings and their applicability in PC and AC settings has not been confirmed.

Only one rule, the Yale Observation Scale (YOS)[10] has been prospectively assessed in four studies,[11-14] of which only two assessed the YOS in the intended age group of 3 to 36 months.[12, 14]

We also identified two national guidelines for the assessment of feverish children (Guideline on Feverish Illness in Children by the National Institute for Health and Clinical Excellence (NICE)[15] and the guidelines from the Dutch College of General Practitioners (NHG)).[16] The NICE traffic light system distinguishes between red features that require immediate referral to paediatric specialist care and amber features that can either require providing parents with a safety net or referral to paediatrics for further assessment.

A focused literature search identified an additional clinical prediction rule published after this review: an emergency-department (ED) rule[17] to diagnose pneumonia, UTI, or bacteraemia (**Table 1.2a-b**)**.**

Although some of these guidelines (NICE guidelines, NHG alarm symptoms) are often used in clinical practice, very little external validation to support their use in practice has been performed in new and independent populations.[18] This raises questions about the robustness of the rules and their generalizability.

The aim of this study was to examine the diagnostic accuracy both of the clinical prediction rules identified by the systematic review and of the evidence-based guidelines, using retrospective external validations on individual patient datasets from ambulatory paediatric settings including PC and ED settings from three European countries.

Table 1.2a: Details of clinical prediction rules and guidelines identified in the systematic review [3]

Clinical Prediction Rule	Clinical features						Age Range	Derivation study
All serious infections								
Yale Observation Scale	quality of cry	reaction to parents' stimulation	state variation	colour	hydration	response to social overtures	3 to 35 months	McCarthy et al.[10]
values	Strong OR not crying 1 Whimpering 3 Weak 5	Cries briefly 1 Cries off and on 3 Continual cry 5	Stays awake 1 Awakes with stimulation 3 Falls to sleep 5	Pink 1 Pale extremities 3 Pale OR cyanotic 5	Skin normal 1 Dry mouth 3 Skin doughy 5	Smiles OR Alerts 1 Brief smile OR alerts briefly 3 No smile OR face anxious 5		
	calculate the sum of all six feature values (cut-offs used in literature: 8, 9 or 10)							
Four-step Decision Tree	clinician gut feeling that something is wrong	dyspnoea	temperature > 39.95°C	diarrhoea in children aged 15-25 months			1 month to 16 years	Van den Bruel et al.[7]
values	No 0 Yes or unknown 1	No or unknown 0 Yes 1	<39.95°C 0 >39.95° C 1	No or unknown 0 Yes 1				
	if yes to any of these four sequential features							
Pneumonia								
Pneumonia Rule n°1	parental concern illness is different	shortness of breath					1 month to 16 years	Van den Bruel et al.[7]
values	if yes to any of these two features							
Pneumonia Rule n°2	clinician concern illness is different	shortness of breath					1 month to 16 years	Van den Bruel et al.[7]
values	if yes to any of these two features							
Meningitis								
Meningitis Rule n°1	any abnormal neurological finding	sought care < 48hrs					3 to 52 months	Offringa et al.[26]
values	if yes to any of these two features							
Meningitis Rule n°2	petechial rash	nuchal rigidity	coma				6 months to 6 years	Joffe et al.[27]
values	if yes to any of these three features							
Gastroenteritis with dehydration								
Gastroenteritis Rule n°1	absent tears	dry mucous membranes	ill appearance	poor peripheral circulation			1 month to 5 years	Gorelick et al.[28]
values	if yes to any two of these four features							

Age range: intended age range for the clinical prediction rule

Table 1.2b: Details of clinical prediction rules and guidelines identified in the systematic review [3]

Clinical guideline	Clinical features								Age Range	Derivation study
Fever guidelines										
NICE traffic light system	colour	activity	respiratory	hydration	other				1 month to 5 years	NICE: Feverish Illness in Children[15]
amber traffic lights	- pallor	- not responding to social cues - wakes only with prolonged stimulation - decreased activity - no smile	- nasal flaring - tachypnoea (age 6-12 months: RR >50/min; age >12 months: RR >40/min) - O_2 saturation ≤ 95% - crackles	- dry mucous membranes - poor feeding in infants - CRT ≥ 3 seconds - reduced urine output	- fever for ≥5 days - swelling of a limb or joint - non-weight bearing limb/not using extremity - a new lump >2 cm					
red traffic lights	- pale/mottled/ ashen/blue	- no response to social cues - appears ill to doctor - does not wake or if roused does not stay awake - weak high-pitched or continuous cry	- grunting - tachypnoea (>60/min) - moderate/severe chest indrawing	- reduced skin turgor	- age 0-3 months, temp ≥38°C - age 3-6 months, temp ≥39°C - non-blanching rash - bulging fontanel - neck stiffness - status epilepticus - focal neurological signs - focal seizures - bile-stained vomiting					
values	if yes to any amber or red traffic light feature of these 5 categories									
NHG alarm symptoms	seriously ill	disturbed consciousness	persistent vomiting	petechial rash	tachypnoea or dyspnoea	reduced peripheral circulation	pallor or ashen or blue	meningeal irritation	1 month to 16 years	Dutch College of General Practitioners (NHG): Feverish Illness in Children[16]
values	if yes to any of these eight features									

Age range: intended age range for the clinical guideline; CRT: capillary refill time; RR: respiratory rate; temp: temperature

METHODS

Identification of datasets

We included datasets from studies identified in the systematic review,[3] which had been published within the past 10 years, and from expert contacts. The criteria used to select datasets (**Table 1.3**), were design (cohort studies that enrolled children consecutively), sample size (>500 children), participants (children aged 0 to 18 years or subgroups of these), setting (AC defined as general or family practice, paediatric outpatient clinics, paediatric assessment units, or EDs in developed countries), outcome (serious infection), and data availability (agreement to share data) (**Figure 1.1**).

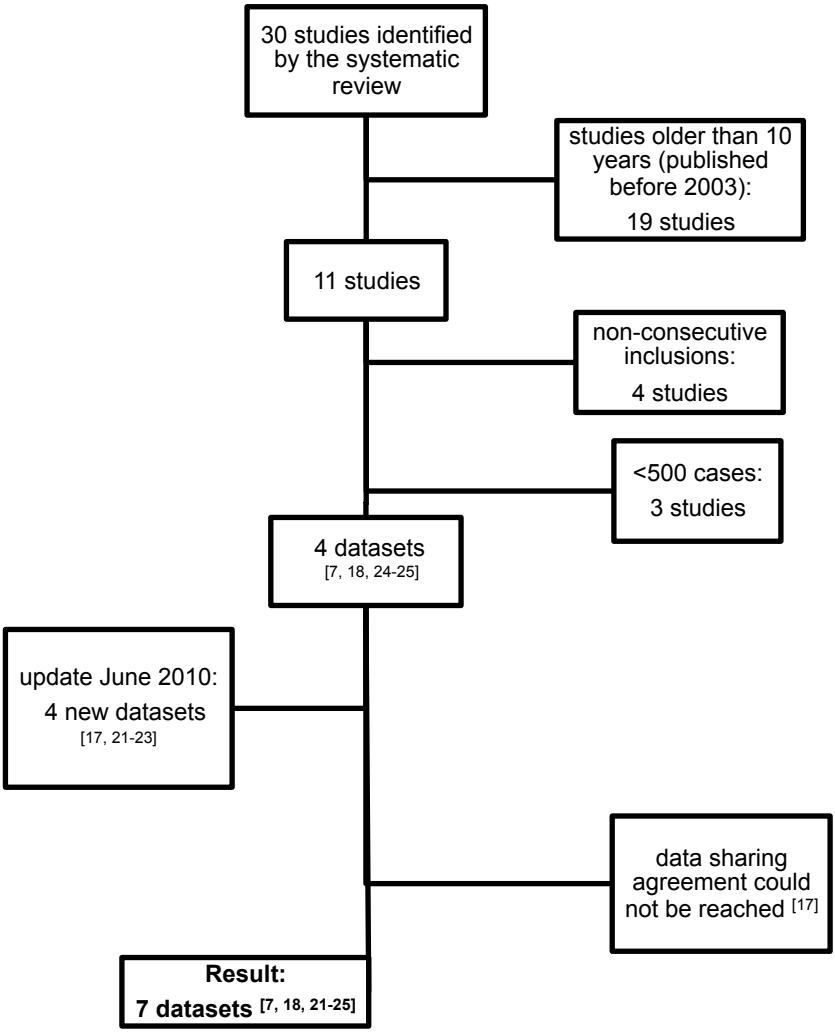

Figure 1.1: Flowchart of dataset inclusion

Table 1.3: Criteria for inclusion and exclusion of datasets in validation analysis

Characteristic	Inclusion	Exclusion
Publication date	Studies published in the past 10 years	Studies published before 2003
Design	Studies that had recorded clinical features; prospective or retrospective cohort study design	Unclear methods
Sample Size	≥ 500 children	< 500 children
Participants	Age between 1 month and 18 years of age; studies including children spanning this age range were included if they reported age (or age could be calculated)	Children with congenital or obtained immunodeficiency Age outside the required range
Setting	Ambulatory care (defined as general or family practice, paediatric outpatient clinics, paediatric assessment units, or emergency departments). Developed countries, defined using the United Nations list, which included Europe, Canada, USA, Australia, New Zealand and Japan	Studies conducted in developing countries Tertiary & secondary care
Outcome	Serious infection, defined as sepsis (including bacteraemia), meningitis, pneumonia, bacterial gastroenteritis with dehydration, osteomyelitis, cellulitis, and complicated urinary-tract infection (positive urine culture and systemic effects such as fever)	Diagnosis other than serious infection
Data availability	Agreement to share data	

Table 1.4: Characteristics of datasets used for external validation of prediction rules

Dataset	Setting	Country	N	Age, years; mean (range)	Prevalence of serious infection % (95% CI)	Inclusion criteria	Exclusion criteria
Van den Bruel *et al.* 2007 [7]	GP/AP/ED	BE	4102	5.0 (0.0 to 16.9)	0.8 (0.5 to 1.1)	Children ≤16 years with acute illness max 5 days	Traumatic or neurological illness, intoxication, psychiatric or behavioral problems without somatic cause or an exacerbation of a chronic condition. No repeated inclusion of same infant within 5 days. Exclusion of physicians if the assumption of consecutive inclusion was probably violated
Roukema *et al.* 2008 [23]	ED	NL	1750	2.9 (0.1 to 15.7)	12.3 (10.8 to 13.9)	All children with fever (>38°C) at ED, without meningeal irritation	Chronic disease, Immunodeficiency
Bleeker *et al.* 2007 [24]	ED	NL	595	0.9 (0.0 to 3.0)	23.0 (19.6 to 26.4)	Children with fever (>38°C) at ED, no clear focus identified after evaluation GP of history by paediatrician	Chronic disease, Immunodeficiency
Monteny *et al.* 2008 [21]	GP	NL	506	2.2 (0.3 to 5.9)	4.0 (2.3 to 5.7)	Children aged 3 months to 6 years, contacting a GP cooperative after hours with fever as the presenting symptom	Language barriers, no repeated inclusion within the previous two weeks
Brent *et al.* 2011 [22]	ED	UK	2777	3.3 (0.0 to 18.4)	5.3 (4.5 to 6.1)	All children presenting with a medical problem to the paediatric emergency-care unit whatever their age	Children who required immediate resuscitation. Comorbidity and chronic illness
Thompson *et al.* 2009 [18]	PAU	UK	700	4.6 (0.0 to 16.0)	37.7 (34.1 to 41.3)	Children aged 3 months to 16 years with suspected acute infection	Children with diseases liable to cause repeated serious bacterial infection, and infections resulting from penetrating trauma
Oostenbrink *et al.* 2004 [25]	ED	NL	593	3.7 (0.1 to 16.1)	43.8 (39.8 to 47.9)	Children aged 1 month to 16 years, meningeal signs at GP, paediatrician-referred or self-referred with neck pain	Comorbidity, ventriculoperitoneal drain

AP: ambulatory paediatric care; BE: Belgium; CI: confidence interval; ED: emergency department; GP: general practice; NL: the Netherlands; PAU: paediatric assessment unit; UK: United Kingdom.

Ethics approval

This research conformed to the Helsinki Declaration and to local legislation. The study authors, agreeing to share data, obtained ethics approval from their regional ethical review boards before the study for the initial data collection of the included datasets.

Processing of included datasets

Direct access to the raw data of each dataset was granted and key characteristics of each of the datasets were extracted (**Table 1.4**). The variables used in each dataset were translated to English if necessary, and the translation, coding, and definition of variables were clarified with the authors of the relevant study.

We used the following criteria to determine which dataset could be used to validate each clinical prediction rule and guideline, and which diagnoses should be included in the composite outcome of serious infection.

- Datasets used to derive a clinical prediction rule were not used to validate the same rule.
- When variables were not entirely identical with the variables of the original clinical prediction rule, we identified proxies where possible. For example, the variable 'dyspnoea' of the 4-step decision tree (4-sSDT) and the pneumonia rule was not recorded in three datasets; we therefore used either 'respiratory distress' or 'chest flaring' as a proxy (**Table 1.5** and **1.6**)
- Based on the number of required variables, whenever one-third or more (fever guidelines), one or more (pneumonia rule, meningitis rule) or two or more (YOS, 4-sDT) of the required variables were not recorded, that dataset was not used for validation of that specific rule. We performed sensitivity analyses as described below.
- Missing data on variables used in the validation were not imputed because the necessary missing-at-random assumption was likely to be incorrect because some of the datasets consisted of routinely collected data from medical records.
- Apart from the approximations used (**Table 1.5** and **1.6**), no alterations of the original data were performed. We report the number of observations available for analysis of each prediction rule after applying these assumptions.
- In contrast to the other dichotomous rules, the YOS generates a sum score. We defined an abnormal result using two pre-selected cut-offs (of 8 or 10).

- Serious infection was defined as sepsis (including bacteraemia), meningitis, pneumonia, osteomyelitis, cellulitis, or complicated UTI.[3] These diagnoses were available for all datasets, and assessment of the diagnoses to ensure comparability of outcomes was discussed with the authors of each study.

The settings in the included datasets were stratified as having low prevalence (LP; 0 to 5%), intermediate prevalence (IP; 5 to 20%) or high prevalence (HP; >20%) of the serious infection(s) of interest (including all serious infections, pneumonia, meningitis) with the clinical assumption that diagnostic goals are different in each setting. In LP settings, clinical prediction rules should have high sensitivity in order to correctly rule out (at a negative likelihood ratio (NLR) of up to 0.2) the target disorder(s) at a reasonable cost in terms of referral or admission rates.[9, 19]

The accuracy of the clinical prediction rules was assessed retrospectively in each of the available prospectively collected datasets by calculating sensitivity, specificity, predictive value, and likelihood ratio (LR). We used dumbbell plots to display the change from pre-test to post-test probabilities.[3] The NICE traffic light system was considered positive if any amber or red traffic light feature was present.

To avoid the risk of influencing diagnostic accuracy by either an arbitrarily chosen number of required variables, or the age range available in each dataset compared with the intended age range of the rule, we performed the following sensitivity analyses after obtaining initial results with the different clinical prediction rules.

Firstly, when a clinical prediction rule was specifically designed for a certain age group (for example, the YOS for children aged 3 to 36 months and the NICE guidelines for children up to 5 years of age), we visually compared the 95% confidence intervals (CIs) of the diagnostic characteristics (sensitivity, specificity, LRs and area under the curve (AUC))[20] in the target age group with the entire age range of the dataset at hand, checking for overlap.

Second, when one or more variables of the original prediction rule were missing, we examined those same diagnostic characteristics in the datasets with no missing variables, to avoid biasing results on the number of missing variables.

Whenever more than one (for the clinical prediction rules) or more than two (for the fever guidelines) original variables were missing, we did not perform sensitivity analysis, based on the rationale that missing two (or more) of a maximum of six variables (for the clinical prediction rules) or three (or more) of a maximum of eight original variables (for the fever guidelines) did not seem clinically sensible. This was discussed and confirmed by all study authors, contributing data to the current study.

Meta-analysis of the pooled results of the multiple external validations was not possible because substantial clinical heterogeneity was found in these datasets, including differences in setting, inclusion criteria, immunization schedules, and definition of serious infection.

Additionally, the small number of included studies would have led to a high level of uncertainty in the estimates of the variances of the random effects for both the bivariate and hierarchical summary receiver operating characteristic models, if heterogeneity were to be explored statistically. Inclusion or exclusion of a single study would affect the convergence of the model greatly.[20]

The individual patient data were analysed in every dataset separately. The translation, re-coding, and data checking were performed by one author (JV), and the results of each step were discussed with all of the other authors.

All analyses were performed with Stata software (version 11.2; Stata Corp., College Station, TX, USA).

Table 1.5: Variables and proxies used for clinical prediction rules validation

Clinical Prediction Rule	used for validation	prevalence	N children	% n/N	variables used (original or proxy)					
All serious infections										
Yale Observation Scale (cutoff > 10)					quality of cry	reaction to parent stimulation	state Variation	colour	hydration	response to social overtures
Van den Bruel et al. [7]	No (no proxies or variables recorded)	Low	3981	-	-	-	-	-	-	-
Monteny et al.[21]	Yes	Low	506	95.3%	+	+	+	+	+	+
Brent et al.[22]	Yes	Intermediate	2777	99.6%	+	-	+	+	+	+
Roukema et al.[23]	No (no proxies or variables recorded)	Intermediate	1750	-	-	-	-	-	-	-
Bleeker et al.[24]	No (no proxies or variables recorded)	High	595	-	-	-	-	-	-	-
Thompson et al.[18]	Yes	High	700	94.7%	+	+	+	+	+	+
Oostenbrink et al.[25]	No (no proxies or variables recorded)	High	593	-	-	-	-	-	-	-
4-step Decision Tree					something is wrong		dyspnoea	temperature	diarrhoea	age
Van den Bruel et al.[a,7]	No (derivation dataset)	Low	3981	-	+		+	+	+	+
Monteny et al.[21]	Yes	Low	506	100.0%	+[b]		+	+	+	+
Brent et al.[22]	Yes	Intermediate	2777	99.5%	+[b]		+[c]	+	+	+
Roukema et al.[23]	Yes	Intermediate	1750	100.0%	+[b]		+[c]	+	+	+
Bleeker et al.[24]	Yes	High	595	100.0%	+[b]		+[c]	+	-	+
Thompson et al.[18]	Yes	High	700	100.0%	+[b]		+	+	+	+
Oostenbrink et al.[25]	No (2 variables not recorded)	High	593	-	+[b]		-	+	-	+
Clinical Diagnostic Model (Craig et al.)					26 items (clinical signs and symptoms)					
Van den Bruel et al. [7]	No (11 variables not recorded)	Low	3981	-	15/26					
Monteny et al.[21]	No (8 variables not recorded)	Low	506	-	18/26					
Brent et al.[22]	No (9 variables not recorded)	Intermediate	2777	-	17/26					
Roukema et al.[23]	No (16 variables not recorded)	Intermediate	1750	-	10/26					
Bleeker et al.[24]	No (18 variables not recorded)	High	595	-	8/26					
Thompson et al.[18]	No (13 variables not recorded)	High	700	-	13/26					
Oostenbrink et al.[25]	No (16 variables not recorded)	High	593	-	10/26					
Pneumonia										
Pneumonia Rule 1					illness is different (parent)		dyspnoea			
Van den Bruel et al.[a,7]	No (derivation dataset)	*Low*	3981	-	+		+			
Monteny et al.[21]	No (1 variable not recorded)	Low	506	-	-		+			
Brent et al.[22]	No (1 variable not recorded)	Intermediate	2777	-	-		+[c]			
Roukema et al.[23]	No (1 variable not recorded)	Intermediate	1750	-	-		+[d]			
Bleeker et al.[24]	No (1 variable not recorded)	Intermediate	595	-	-		+[c]			
Thompson et al.[18]	No (1 variable not recorded)	Intermediate	700	-	-		+			
Oostenbrink et al.[25]	No (2 variables not recorded)	High	593	-	-		-			
Pneumonia Rule 2					something is wrong		dyspnoea			
Van den Bruel et al.[a,7]	No (derivation dataset)	*Low*	3981	-	+		+			
Monteny et al.[22]	Yes	Low	506	100.0%	+[b]		+			
Brent et al.[23]	Yes	Intermediate	2777	78.6%	+[b]		+[c]			
Roukema et al.[24]	Yes	Intermediate	1750	96.1%	+[b]		+[d]			
Bleeker et al.[25]	Yes	Intermediate	595	100.0%	+[b]		+[c]			
Thompson et al.[18]	Yes	Intermediate	700	100.0%	+[b]		+			
Oostenbrink et al.[26]	No (1 variable not recorded)	High	593	-	+[b]		-			
Meningitis										
Meningitis Rule 1					petechiae		nuchal rigidity		coma	
Van den Bruel et al. [7]	Yes	Low	3981	100.0%	+		+[e]		+[f]	
Monteny et al.[21]	No (2 variables not recorded)	Low	506	-	+		-		-	
Thompson et al.[18]	Yes	Low	700	100.0%	+		+		+[f]	
Roukema et al.[23]	No (2 variables not recorded)	Low	1750	-	-		+		-	
Bleeker et al.[24]	No (3 variables not recorded)	Low	595	-	-		-		-	
Brent et al.[22]	Yes	Low	2777	78.2%	+		-		+[f]	
Oostenbrink et al.[25]	Yes	High	593	100.0%	+		+[e]		+[f]	
Meningitis Rule 2					any abnormal neurological findings				sought care < 48 hrs	
Van den Bruel et al. [7]	No (1 variable not recorded)	Low	3981	-	+				-	
Monteny et al.[21]	No (1 variable not recorded)	Low	506	-	+				-	
Thompson et al.[18]	No (1 variable not recorded)	Low	700	-	+				-	
Roukema et al.[23]	No (1 variable not recorded)	Low	1750	-	+				-	
Bleeker et al.[24]	No (2 variables not recorded)	Low	595	-	-				-	
Brent et al.[22]	No (1 variable not recorded)	Low	2777	-	+				-	
Oostenbrink et al.[25]	No (1 variable not recorded)	High	593	-	+				-	
Gastroenteritis with dehydration										
Gastroenteritis rule					dry mucous membranes		poor peripheral circulation		absent tears	ill appearance
Van den Bruel et al. [7]	No (2 variables not recorded)	Low	3981	-	-		+		-	+
Monteny et al.[21]	No (2 variables not recorded)	Low	506	-	-		+		-	+
Brent et al.[22]	No (2 variables not recorded)	Intermediate	2777	-	-		+		-	+
Roukema et al.[23]	No (2 variables not recorded)	Intermediate	1750	-	-		+		-	+
Bleeker et al.[24]	No (2 variables not recorded)	High	595	-	-		+		-	+
Thompson et al.[18]	No (2 variables not recorded)	High	700	-	-		+		-	+
Oostenbrink et al.[25]	No (2 variables not recorded)	High	593	-	-		+		-	+

N: Number of children in dataset; % n/N: Percentage of cases (n) out of all children (N) used for the external validation analysis; [a]Derivation study (italic); [b]'Clinical sick impression' used as proxy for 'physician's gut feeling that something is wrong'; [c]'Respiratory distress' used as proxy for 'dyspnoea'; [d]'Chest flaring' used as proxy for 'dyspnoea'; [e]'Meningeal irritation' used as proxy for 'nuchal rigidity'; [f]'Unconsciousness' used as proxy for 'coma'.

Table 1.6: Variables and proxies used for fever guidelines validation

Fever Guidelines	used for validation	prevalence	N children	% n/N	variables used (original or proxy)					
All serious infections										
NICE (any amber or red traffic light present)					**colour**	**activity**	**respiratory**	**hydration**	**other**	
Van den Bruel et al.[7]	Yes	Low	3981	99.5%	"cyanosis"	"does not smile anymore" "cries differently" "clinical sick impression" "appears drowsy" "decreased consciousness"	"tachypnoea" "decreased breathing sounds" "crepitations on lung auscultation"	"deshydration" "reduced peripheral circulation"	"petechiae" "meningeal irritation" "temperature and age"	
Monteny et al.[21]	Yes	Low	506	100.0%	"pallor" "ashen"	"appears drowsy" "clinical sick impression" "cries continuously" "reduced alertness" "reaction to parents" "Yale social overtures" "reduced social interaction" Yale state variation"	"tachypnoea" "grunting" "nasal flaring"	"poor feeding" "reduced urinary output" "capillary refill time" "deshydration"	"temperature and age" "bulging fontanelle" "focal neurological signs" "neck stiffness" "non-blanching rash"	
Brent et al.[22]	Yes	Intermediate	2777	100.0%	"colour"	"clinical sick impression" "response to social cues" "state variation"	"nasal flaring"; "grunting"; "tachypnoea"; "oxygen saturation"; "apnoea"; "use of accessory muscles of respiration"; "poor air entry"; "localised or generalised crackles"	"deshydration" "capillary refill time"	"petechial rash" "temperature and age"	
Roukema et al.[23]	Yes	Intermediate	1750	71.2%	"colour"	"clinical sick impression"	"tachypnoea" "oxygen saturation" "chest indrawing"	"capillary refill time"	"age and temperature" "nuchal rigidity"	
Bleeker et al.[24]	Yes	High	595	99.3%	"colour"	"clinical sick impression" "decreased consciousness" "cries continuously"	"dyspnoea" "crepitations on lung auscultation"	"reduced peripheral circulation" "poor feeding" "reduced urinary output"	"age and temperature" "duration of fever" "bulging fontanelle"	
Thompson et al.[16]	Yes	High	700	100.0%	"NICE colour"	"NICE Activity"	"NICE Respiratory"	"NICE Hydration"	"NICE Other"	
Oostenbrink et al.[25]	Yes	High	593	100.0%	"colour" "cyanosis"	"clinical sick impression" "decreased consciousness" "appears drowsy" "cries continuously"	"tachypnoea" "oxygen saturation" "chest indrawing"	"hydration" "capillary refill time"	"age and temperature"; "duration of fever"; "bulging fontanelle"; "focal neurological signs"; "nuchal rigidity"; "petechial rash"	
NHG alarm symptoms					**seriously ill**	**disturbed consciousness**	**persistent vomiting**	**petechiae**	**tachypnea or dyspnea**	**reduced peripheral circulation**	**pallor or ashen or blue**	**meningeal irritation**
Van den Bruel et al.[7]	Yes	Low	3981	100.0%	"clinical sick impression"	"decreased consciousness" "appears drowsy"	-	"petechiae"	"tachypnoea" "dyspnoea"	"reduced peripheral circulation"	"cyanosis"	"meningeal irritation"
Monteny et al.[21]	Yes	Low	506	100.0%	"clinical sick impression"	"appears drowsy" "appears confused" "reduced alertness"	"persistent vomiting"	"non-blanching rash"	"tachypnoea" "dyspnoea"	"capillary refill time" "deshydration"	"pallor" "ashen"	"focal neurological signs" "neck stiffness"
Brent et al.[22]	Yes	Intermediate	2777	100.0%	"clinical sick impression"	"result of AVPU scale"	-	"petechial rash"	"tachypnoea" "dyspnoea" "apnoea"	"capillary refill time" "deshydration"	"colour"	-
Roukema et al.[23]	Yes	Intermediate	1750	100.0%	"clinical sick impression"	-	-	-	"tachypnoea" "chest indrawing"	"hydration" "capillary refill time"	"colour"	"nuchal rigidity"
Bleeker et al.[24]	Yes	High	595	100.0%	"clinical sick impression"	"decreased consciousness"	-	-	"dyspnoea"	"reduced peripheral circulation"	"colour"	-
Thompson et al.[16]	Yes	High	700	100.0%	"clinical sick impression"	"decreased consciousness" "appears drowsy" "appears confused"	-	"non-blanching rash"	"tachypnoea" "dyspnoea"	"capillary refill time" "deshydration"	"colour"	"neck stiffness"
Oostenbrink et al.[25]	Yes	High	593	100.0%	"clinical sick impression"	"decreased consciousness" "appears drowsy"	-	"petechial rash"	"tachypnoea"	"capillary refill time" "reduced peripheral circulation"	"colour" "cyanosis"	"focal neurological signs" "nuchal rigidity"

N: number of children in dataset; % n/N: percentage of cases (n) out of all children (N) used for the external validation analysis

RESULTS

Included datasets

We obtained seven datasets providing data on 11023 children: two LP datasets from general practice,[7, 21] two IP datasets from EDs [22, 23] and three HP datasets from EDs [24, 25] or paediatric assessment units [18] in the UK (n = 2), the Netherlands (n = 4) and Belgium (n = 1) (**Figure 1.1**, **Table 1.3**). Children were included based on presence of fever, [21, 23, 24] acute illness, [7, 22] or acute infection,[18] or on referral for meningeal signs.[25] Children with various comorbidities were excluded in six studies, and one study excluded children who required immediate resuscitation. The outcome in all studies included sepsis, meningitis, pneumonia, and complicated UTI as part of the outcome variables. Osteomyelitis and cellulitis were explicitly mentioned in five and three datasets, respectively. The mean age ranged from 0.94 to 5.0 years, and prevalence of serious infection from 0.8 to 43.8%.

Clinical predictors included in the datasets

Most datasets included basic demographic characteristics such as age, duration, and severity of illness, as well as referral status. Temperature was recorded in all datasets (with missing data rates ranging from 0 to 18%), heart rate in five datasets (missing in 2 to 48%), capillary refill time in five (missing in 2 to 48%), respiratory rate in four (missing in 15 to 53%), and oxygen saturation in four (missing in 4 to 74%).

Validation of the 4-sDT [7] was possible in five datasets,[18, 21-24] of which four had all variables present using 'clinical sick impression' as a proxy for 'physician's gut feeling that something is wrong', and 'respiratory distress' or 'chest flaring' as a proxy for 'dyspnoea' (**Table 1.5**). Because the variable 'diarrhoea' was missing in one dataset,[25] we performed a sensitivity analysis comparing the results of the three remaining variables, as noted below.

Five datasets [18, 21-24] were available for one pneumonia rule,[7] developed in PC settings, with 'sick impression to clinician' as a proxy for the 'physician's gut feeling that something is wrong' and 'nasal flaring' for 'dyspnoea'. A second pneumonia rule, derived in the same dataset,[7] which included 'respiratory distress' and 'parental concern the illness is different' could not be validated, as the latter variable was not recorded in any of the validation datasets.

A meningitis rule, derived by Offringa et al. [26] for children in the ED, was validated in three datasets.[7, 18, 25] Because all items except 'nuchal rigidity' were present in one additional dataset,[22] we performed a sensitivity analysis comparing the results of the two remaining variables, eventually excluding this dataset from the analysis, as noted below. A second meningitis rule could not be validated because of the absence of its key variables in these datasets.[27]

For the YOS,[10] developed in secondary care, three datasets had recorded variables used in the original Yale scoring [18, 21, 22] (**Table 1.5**). Because the YOS item 'reaction to parent stimulation' was missing in one dataset,[22] we performed a sensitivity analysis comparing the results of the five remaining YOS items, as noted below. None of the datasets included sufficient variables to validate the prediction rule to identify gastro-enteritis with dehydration developed by Gorelick et al.,[28] or the prediction rule developed by Craig et al.[17]
The NICE guideline for feverish illness in children and the NHG alarm symptoms [15, 16] were validated in four [18, 21, 22, 25] and five [7, 18, 21, 22, 25] datasets, respectively.

Validation results
The characteristics of diagnostic accuracy, according to prevalence, are shown for all clinical prediction rules (**Figure 1.2**, **Figure 1.3**).

Low-prevalence settings
The 4-sDT had a sensitivity of 90% (95% CI 68 to 99%) and a specificity of 85% (95% CI 84 to 86%) in the single LP dataset available for validation, with false-positive test results (for example, no serious infection present) in 54% of all children examined.[21] The sensitivities of the pneumonia rule were 94% (95% CI 71 to 100%) and 92% (95% CI 86 to 96%) in two datasets, with specificities of less than 45%, resulting in 54% and 56% false-positive test results.[21, 22] Validation of the meningitis rule in two LP datasets [7, 18] resulted in sensitivities ranging from 33% (PC dataset) to 100% (secondary care dataset with a LP for meningitis) with specificities ranging from 90 to 99%. The YOS, with cut-offs of 8 and 10, provided sensitivities below 46% in one LP dataset,[21] but had a specificity greater than 84%. The NICE 'traffic light' system with any amber or red sign present, and the NHG alarm symptoms were extremely sensitive (100%) with specificity from 1 to 85%, testing as false positive in 90 to 95% of all children in one LP dataset.[21]

Intermediate-prevalence settings
The 4-sDT provided moderate sensitivities of 76% (95% CI 69 to 81%) and 88% (95% CI 82 to 93%), in two IP settings [22, 23] (with specificities below 40%). The pneumonia rule had sensitivities ranging from 66 to 82% in two datasets [23, 24] but in a third dataset [18] with the highest prevalence (11%) of pneumonia, sensitivity was only 27% (95% CI 17 to 39%) with a specificity of 89% (95% CI 86 to 91%). The YOS, with cut-off values of 8 and 10, provided sensitivities of less than 41% in one IP dataset,[22] and a specificity greater than 84%. Finally, the NICE guideline and NHG alarm symptoms had high sensitivity (97 to 100%) in one IP setting [22] with specificities below 27%.

High-*prevalence settings*
In one HP setting,[24] the 4-sDT had a sensitivity of 89% (95% CI 83 to 94%) with specificity of 32% (95% CI 28 to 37%). However, sensitivity was only 23% (95% CI 18 to 29%) with specificity of 86% (95% CI 83 to 89%) in a paediatric assessment unit.[18] In one study [26] that included children with meningeal signs identified by the referring physician, the meningitis rule showed high sensitivity, at 96% (95% CI 92 to 98%) and specificity of 49% (95% CI 44 to 54%). The Yale score, with cut-offs of 8 and 10, provided sensitivities of less than 30% in one HP dataset [18], and specificity above 81%. Finally, both NICE guideline and NHG alarm symptoms had sensitivities ranging from 87 to 99% in two HP datasets [18, 25] with specificities ranging from 2 to 29%.

Sensitivity analyses
Comparing the 95% CIs, we found similar results for the diagnostic characteristics of the YOS and the NICE guidelines in children of all ages as well as in children for whom the rules were originally designed (3 to 35 months and up to 5 years, respectively) (**Table 1.7**).

Comparing the results of the datasets in which the complete prediction rule could be validated with those of the datasets with one or two missing variables (five items of the YOS, four items of the 4-sDT, and six items of the NHG alarm symptoms), all diagnostic characteristics were found to be similar through visual comparison of the 95% CIs (**Table 1.7**).

By contrast, dropping 'nuchal rigidity' from the meningitis rule resulted in a lower sensitivity (67% (95% CI 9 to 99%) versus 100% (95% CI 29 to 100%) when all three variables were considered) in one dataset,[18] eliminating one additional dataset, which had only two out of three original variables available, for further use in the validation.[22]

clinical prediction rule		dataset	n/N[a]	% test positive[b]	% sensitivity (95% CI)	% specificity (95% CI)	Likelihoodratio (95% CI) positive	Likelihoodratio (95% CI) negative	Probability of illness (%)
Low prevalence									
4-step Decision Tree[c]		*Van den Bruel et al.*[d][7]	*31/3981*	12.2	*96.8 (83.3-99.9)*	*88.5 (87.5-89.5)*	*8.42 (7.56-9.38)*	*0.04 (0.05-0.25)*	
		Van den Bruel et al.[e][7]	31/3981	15.3	90.3 (74.2-98.0)	85.3 (84.1-86.4)	6.13 (5.34-7.03)	0.11 (0.04-0.33)	
		Monteny et al.[21]	20/506	57.7	90.0 (68.3-98.8)	43.6 (39.2-48.2)	1.60 (1.35-1.88)	0.23 (0.06-0.86)	
Pneumonia Rule[f]		*Van den Bruel et al.*[d][7]	*16/3981*	*11.0*	*87.5 (61.7-98.4)*	*89.3 (88.3-90.3)*	*8.18 (6.66-10.1)*	*0.14 (0.04-0.51)*	
		Monteny et al.[21]	17/506	56.7	94.1 (71.3-99.9)	44.6 (40.1-49.1)	1.70 (1.47-1.96)	0.13 (0.02-0.89)	
		Brent et al.[22]	131/2687	60.2	92.4 (86.4-96.3)	41.4 (39.5-43.4)	1.58 (1.49-1.67)	0.18 (0.10-0.34)	
Meningitis Rule[g]		Thompson et al.[18]	3/700	10.4	100 (29.2-100)	90.0 (87.5-92.1)	8.66 (5.63-13.3)	0.14 (0.01-1.86)	
		Van den Bruel et al.[7]	9/3981	0.9	33.3 (7.49-70.1)	99.1 (98.8-99.4)	38.9 (14.6-104)	0.67 (0.42-1.07)	
Yale Observation Scal	(cutoff > 8)	Monteny et al.[21]	13/482	16.6	46.2 (19.2-74.9)	84.2 (80.6-87.4)	2.93 (1.57-5.46)	0.64 (0.39-1.06)	
	(cutoff > 10)	Monteny et al.[21]	13/482	7.3	23.1 (5.04-53.8)	93.2 (90.5-95.3)	3.38 (1.19-9.64)	0.83 (0.61-1.11)	
Intermediate prevalence									
4-step Decision Tree[c]		Brent et al.[22]	148/2757	61.3	87.8 (81.5-92.6)	40.2 (38.3-42.1)	1.47 (1.37-1.57)	0.30 (0.20-0.47)	
		Roukema et al.[23]	216/1750	65.2	75.5 (69.2-81.0)	36.2 (33.8-38.7)	1.18 (1.09-1.29)	0.68 (0.53-0.86)	
Pneumonia Rule[f]		Roukema et al.[23]	114/1750	57.5	65.8 (56.3-74.4)	43.1 (40.7-45.5)	1.16 (1.01-1.33)	0.79 (0.61-1.03)	
		Bleeker et al.[24]	54/595	57	81.5 (68.6-90.7)	45.5 (41.2-49.8)	1.49 (1.29-1.73)	0.41 (0.23-0.72)	
		Thompson et al.[18]	67/700	12.4	26.9 (16.8-39.1)	89.1 (86.4-91.4)	2.46 (1.57-3.88)	0.82 (0.71-0.95)	
Yale Observation Scal	(cutoff > 8)	Brent et al.[22]	148/2765	17.5	40.5 (32.6-48.9)	83.9 (82.3-85.2)	2.50 (2.02-3.10)	0.71 (0.62-0.81)	
	(cutoff > 10)	Brent et al.[22]	148/2765	6.4	22.3 (15.9-29.9)	94.5 (93.6-95.3)	4.05 (2.88-5.69)	0.82 (0.75-0.90)	
High prevalence									
4-step Decision Tree[c]		Bleeker et al.[24]	137/595	72.6	89.1 (82.6-93.7)	32.3 (28.0-36.8)	1.32 (1.21-1.43)	0.34 (0.21-0.56)	
		Thompson et al.[18]	264/700	17.1	23.0 (18.0-28.6)	86.3 (82.8-89.4)	1.68 (1.22-2.32)	0.89 (0.83-0.96)	
Meningitis Rule[g]		Oostenbrink et al.[25]	221/593	68	95.9 (92.4-98.1)	48.7 (43.5-53.9)	1.87 (1.69-2.07)	0.08 (0.04-0.16)	
Yale Observation Scal	(cutoff > 8)	Thompson et al.[18]	241/663	23.1	30.3 (24.6-36.5)	81.0 (77.0-84.7)	1.60 (1.21-2.10)	0.86 (0.78-0.95)	
	(cutoff > 10)	Thompson et al.[18]	241/663	14.3	19.5 (14.7-25.1)	88.6 (85.2-91.5)	1.71 (1.18-2.48)	0.91 (0.85-0.98)	

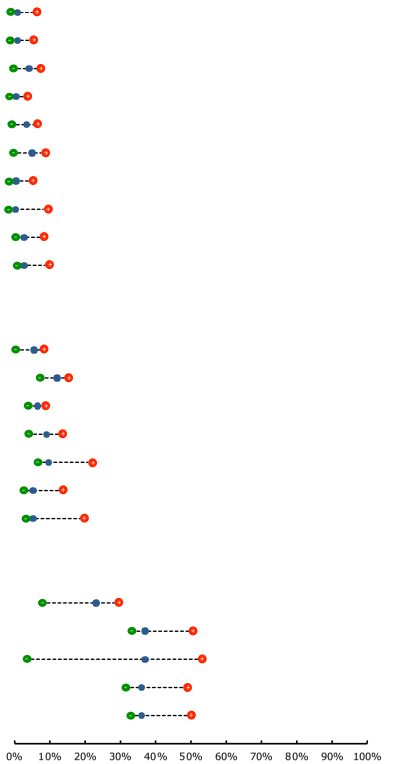

Figure 1.2: Results of external validation of clinical prediction rules to rule in or rule out serious infection

[a]Number of cases (n) out of the total population of all children (N); [b]Percentage testing positive in all included children; [c]If yes to any of four sequential questions: 1) clinical instinct that something is wrong, 2) dyspnoea, 3) temperature greater than 39.5°C, 4) diarrhoea in children aged 15 to 29 months; [d]Derivation study (italic); [e]'clinical instinct that something is wrong' replaced by 'clinical impression'; [f]If yes to any of the following: 1) shortness of breath, 2) clinicians concern; [g]If yes to any of the following: 1) petechial rash, 2) nuchal rigidity, 3) coma; probability of serious infection (in percentage) before testing (plain dot), after a positive test result (red dot with plus sign) increasing the probability of infection and after a negative test result (green dot with minus sign) decreasing the probability of infection.

clinical prediction rule	dataset	n/N[a]	% test positive[b]	% sensitivity (95% CI)	% specificity (95% CI)	Likelihoodratio (95% CI) positive	Likelihoodratio (95% CI) negative	Probability of illness (%)
Low prevalence								
NICE guidelines[c]	Monteny et al.[21]	20/506	99.0	100 (83.2-100)	1.03 (0.34-2.38)	0.99 (0.92-1.06)	2.11 (0.12-36.9)	
NHG alarm symptoms[d]	Van den Bruel et al.[7]	31/3981	15.5	80.6 (62.5-92.5)	85 (83.9-86.1)	5.38 (4.46-6.49)	0.23 (0.11-0.47)	
	Monteny et al.[21]	20/506	94.3	100 (83.2-100)	5.97 (4.03-8.46)	1.04 (0.97-1.12)	0.39 (0.25-6.22)	
Intermediate prevalence								
NICE guidelines[c]	Brent et al.[22]	148/2777	74.5	97.3 (93.2-99.3)	26.7 (25.1-28.5)	1.33 (1.28-1.38)	0.10 (0.04-0.27)	
NHG alarm symptoms[d]	Brent et al.[22]	148/2777	80.6	100 (97.5-100)	20.5 (19.0-22.1)	1.25 (1.23-1.28)	0.02 (0.00-0.26)	
High prevalence								
NICE guidelines[c]	Thompson et al.[18]	264/700	77.3	87.1 (82.5-90.9)	28.7 (24.5-33.2)	1.22 (1.13-1.32)	0.45 (0.32-0.64)	
	Oostenbrink et al.[25]	260/593	98.1	98.5 (96.1-99.6)	2.10 (0.85-4.28)	1.01 (0.98-1.03)	0.73 (0.22-2.47)	
NHG alarm symptoms[d]	Thompson et al.[18]	264/700	80.6	90.9 (86.8-94.1)	25.7 (21.6-30.1)	1.22 (1.14-1.31)	0.35 (0.23-0.54)	
	Oostenbrink et al.[25]	260/593	98.1	98.1 (95.6-99.4)	1.80 (0.66-3.88)	1.00 (0.98-1.02)	1.07 (0.33-3.46)	

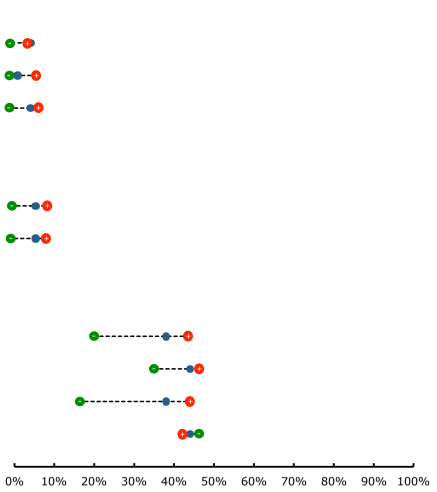

Figure 1.3: Results of external validation of the evidence-based clinical guidelines for management of fever

[a]Number of cases (n) out of the total population of all children (N); [b]Percentage testing positive in all included children; [c]'Traffic light' system of clinical features that are designed to be used to assess the risk of serious infection, and to provide clinical guidance for actions needed according to these categories; [d]Alarm symptoms at clinical examination: seriously ill impression, reduced consciousness, persistent vomiting, petechial rash, tachypnoea and/or dyspnoea, reduced peripheral circulation, pallor, and signs of meningeal irritation; probability of illness (in percentage) before testing (plain dot), after a positive test result (red dot with plus sign) and after a negative test result (green dot with minus sign).

Table 1.7: Sensitivity analyses

clinical prediction rule	conditions	% sensitivity (95% CI)	% specificity (95% CI)	Likelihoodratio (95% CI) positive	Likelihoodratio (95% CI) negative	Area under the curve (95% CI)
Yale Observation Scale (cutoff > 10)						
Monteny et al.[21]	all 6 items available	23.1 (5.04-53.8)	93.2 (90.5-95.3)	3.38 (1.19-9.64)	0.83 (0.61-1.11)	0.58 (0.46-0.70)
	5 items available (minus "reaction to parent stimulation")	15.4 (1.92-45.4)	94.0 (91.5-96.0)	2.58 (0.69-9.69)	0.90 (0.71-1.14)	0.55 (0.44-0.65)
	limited to age range 3 to 36 months	37.5 (8.52-75.5)	92.6 (89.2-95.1)	5.06 (1.91-13.3)	0.68 (0.39-1.16)	0.56 (0.47-0.83)
Brent et al.[22]	all 6 items available	-	-	-	-	-
	5 items available (minus "reaction to parent stimulation")	22.3 (15.9-29.9)	94.5 (93.6-95.3)	4.05 (2.88-5.69)	0.82 (0.75-0.90)	0.58 (0.55-0.62)
	limited to age range 3 to 36 months	24.6 (14.5-37.3)	93.8 (92.7-94.9)	3.06 (1.89-4.95)	0.82 (0.71-0.95)	0.58 (0.53-0.64)
Thompson et al.[18]	all 6 items available	19.5 (14.7-25.1)	88.6 (85.2-91.5)	1.71 (1.18-2.48)	0.91 (0.85-0.98)	0.54 (0.51-0.57)
	5 items available (minus "reaction to parent stimulation")	12.1 (8.31-21.8)	90.3 (84.9-92.8)	1.91 (1.16-3.13)	0.94 (0.89-0.99)	0.53 (0.51-0.55)
	limited to age range 3 to 36 months	20.8 (11.2-30.3)	85.3 (79.1-90.6)	1.42 (0.83-2.41)	0.93 (0.82-1.05)	0.57 (0.51-0.63)
4-step decision tree						
Van den Bruel et al.[7]	all 4 items available	90.3 (74.2-98.0)	85.3 (84.1-86.4)	6.13 (5.34-7.03)	0.11 (0.04-0.33)	0.88 (0.82-0.93)
	3 items available (minus "diarrhoea")	90.3 (74.2-98.0)	82.8 (81.9-85.6)	5.72 (5.21-6.32)	0.13 (0.04-0.38)	0.82 (0.77-0.88)
Monteny et al.[21]	all 4 items available	90.0 (68.3-98.8)	43.6 (39.2-48.2)	1.60 (1.35-1.88)	0.23 (0.06-0.86)	0.67 (0.60-0.74)
	3 items available (minus "diarrhoea")	90.0 (68.3-98.8)	40.6 (36.5-45.2)	1.43 (1.23-1.65)	0.31 (0.08-1.17)	0.61 (0.54-0.68)
Brent et al.[22]	all 4 items available	87.8 (81.5-92.6)	40.2 (38.3-42.1)	1.47 (1.37-1.57)	0.30 (0.20-0.47)	0.64 (0.61-0.67)
	3 items available (minus "diarrhoea")	91.3 (86.6-93.8)	38.4 (36.5-40.3)	1.52 (1.45-1.59)	0.23 (0.17-0.36)	0.67 (0.63-0.69)
Thompson et al.[18]	all 4 items available	23.0 (18.0-28.6)	86.3 (82.8-89.4)	1.68 (1.22-2.32)	0.89 (0.83-0.96)	0.55 (0.52-0.58)
	3 items available (minus "diarrhoea")	29.0 (22.9-35.5)	85.7 (82.3-88.7)	2.10 (1.56-2.83)	0.82 (0.74-0.90)	0.58 (0.54-0.61)
Bleeker et al.[24]	all 4 items available	-	-	-	-	-
	3 items available (minus "diarrhoea")	89.1 (82.6-93.7)	32.3 (28.0-36.8)	1.32 (1.21-1.43)	0.34 (0.21-0.56)	0.61 (0.57-0.64)
Roukema et al.[23]	all 4 items available	75.5 (69.2-81.0)	36.2 (33.8-38.7)	1.18 (1.09-1.29)	0.68 (0.53-0.86)	0.56 (0.53-0.59)
	3 items available (minus "diarrhoea")	79.2 (73.1-84.4)	34.0 (31.7-36.4)	1.12 (1.03-1.2)	0.72 (0.55-0.94)	0.54 (0.51-0.57)
Meningitis Rule 1						
Van den Bruel et al.[7]	all 3 items available	33.3 (7.49-70.1)	99.1 (98.8-99.4)	38.9 (14.6-104)	0.67 (0.42-1.07)	0.66 (0.50-0.83)
	2 items available (minus "nuchal rigidity")	22.2 (2.81-60.0)	99.2 (98.9-99.5)	28.5 (7.98-102)	0.78 (0.55-1.11)	0.61 (0.46-0.75)
Brent et al.[22]	all 3 items available	-	-	-	-	-
	2 items available (minus "nuchal rigidity")	45.2 (27.3-64.0)	97.9 (97.3-98.4)	21.8 (13.7-34.8)	0.56 (0.41-0.77)	0.72 (0.63-0.81)
Thompson et al.[18]	all 3 items available	100 (29.2-100)	90.0 (87.5-92.1)	8.66 (5.63-13.3)	0.14 (0.01-1.86)	0.95 (0.94-0.96)
	2 items available (minus "nuchal rigidity")	66.7 (9.43-99.2)	92.1 (89.9-94.0)	8.45 (3.65-19.6)	0.36 (0.07-1.79)	0.79 (0.47-1.00)
Oostenbrink et al.[25]	all 3 items available	95.9 (92.4-98.1)	48.7 (43.5-53.9)	1.87 (1.69-2.07)	0.08 (0.04-0.16)	0.72 (0.69-0.75)
	2 items available (minus "nuchal rigidity")	53.4 (46.6-60.1)	91.1 (87.8-93.8)	6.02 (4.25-8.53)	0.51 (0.44-0.59)	0.72 (0.69-0.76)
NICE guidelines						
Monteny et al.[21]	all ages	100 (83.2-100)	1.03 (0.34-2.38)	0.99 (0.92-1.06)	2.11 (0.12-36.9)	0.51 (0.50-0.51)
	limited to age range 0 to 5 years	100 (82.4-100)	1.08 (0.35-2.50)	0.99 (0.92-1.06)	2.11 (0.12-36.8)	0.51 (0.50-0.51)
Brent et al.[22]	all ages	97.3 (93.2-99.3)	26.7 (25.1-28.5)	1.33 (1.28-1.38)	0.10 (0.04-0.27)	0.65 (0.63-0.66)
	limited to age range 0 to 5 years	99.1 (95.4-100)	29.4 (26.4-32.6)	1.37 (1.32-1.43)	0.04 (0.00-0.41)	0.65 (0.63-0.66)
Thompson et al.[18]	all ages	87.1 (82.5-90.9)	28.7 (24.5-33.2)	1.22 (1.13-1.32)	0.45 (0.32-0.64)	0.58 (0.55-0.61)
	limited to age range 0 to 5 years	89.0 (83.3-93.2)	25.6 (20.7-30.9)	1.20 (1.10-1.30)	0.43 (0.27-0.69)	0.57 (0.54-0.61)
Oostenbrink et al.[25]	all ages	98.5 (96.1-99.6)	2.10 (0.85-4.28)	1.01 (0.98-1.03)	0.73 (0.22-2.47)	0.50 (0.49-0.51)
	limited to age range 0 to 5 years	99.4 (96.8-100)	2.37 (0.88-5.09)	1.02 (0.99-1.04)	0.25 (0.03-2.04)	0.51 (0.50-0.53)
NHG alarm symptoms						
Monteny et al.[21]	all 8 items available	100 (83.2-100)	5.97 (4.03-8.46)	1.04 (0.97-1.12)	0.39 (0.25-6.22)	0.53 (0.52-0.54)
	6 items available (minus "persistent vomiting" & "nuchal rigidity")	100 (83.2-100)	5.97 (4.03-8.46)	1.04 (0.97-1.12)	0.39 (0.25-6.22)	0.53 (0.52-0.54)
Van den Bruel et al.[7]	all 8 items available	80.6 (62.5-92.5)	85 (83.9-86.1)	5.38 (4.46-6.49)	0.23 (0.11-0.47)	0.83 (0.76-0.90)
	6 items available (minus "persistent vomiting" & "nuchal rigidity")	80.6 (62.5-92.5)	85.3 (84.1-86.4)	5.47 (4.53-6.61)	0.23 (0.11-0.47)	0.83 (0.76-0.90)
Brent et al.[22]	all 8 items available	-	-	-	-	-
	6 items available (minus "persistent vomiting" & "nuchal rigidity")	100 (97.5-100)	20.5 (19.0-22.1)	1.25 (1.23-1.28)	0.02 (0.00-0.26)	0.60 (0.63-0.81)
Thompson et al.[18]	all 8 items available	90.9 (86.8-94.1)	25.7 (21.6-30.1)	1.22 (1.14-1.31)	0.35 (0.23-0.54)	0.50 (0.49-0.51)
	6 items available (minus "persistent vomiting" & "nuchal rigidity")	90.9 (86.8-94.1)	25.7 (21.6-30.1)	1.22 (1.14-1.31)	0.35 (0.23-0.54)	0.50 (0.49-0.51)
Oostenbrink et al.[25]	all 8 items available	98.1 (95.6-99.4)	1.80 (0.66-3.88)	1.00 (0.98-1.02)	1.07 (0.33-3.46)	0.58 (0.56-0.61)
	6 items available (minus "persistent vomiting" & "nuchal rigidity")	95.8 (92.4-98.3)	3.50 (1.54-6.32)	1.00 (0.96-1.03)	1.11 (0.54-2.29)	0.58 (0.56-0.61)

CI: confidence interval; underlined: 95% CIs not overlapping

DISCUSSION

Main findings

None of the clinical prediction rules examined in this study provided adequate diagnostic accuracy. The best performing clinical prediction rule for ruling out serious infection in an LP setting was the 4-sDT, which uses the physician's gut feeling, the patient's temperature, and presence of dyspnoea and diarrhoea in a specific age range.[7] Sensitivity was lower than that reported in the original study, possibly explained by our use of 'clinical impression' as a proxy for 'physician's gut feeling' which has been reported to be of lower diagnostic value.[3]

Both the NICE guideline and the NHG alarm symptoms had high sensitivity in both LP and IP settings, suggesting possible clinical value for ruling out serious infections in children presenting in these settings. However, large numbers of children were flagged as potentially having a serious infection. If the prediction rules were to be used in clinical practice, additional clinical assessment, additional testing, or review at a later stage would be necessary to avoid inappropriate referrals or hospital admissions.

For the well-known YOS, all sensitivities were low, which is similar to the results of a previously reported pooled sensitivity based on the meta-analysis of seven studies.[3]

Other disease-specific rules (pneumonia and meningitis) had acceptable sensitivities only in the LP settings, indicating value as rule-out tests. However, the percentage of false positives was too high in all datasets, apart from one IP dataset, probably due to the higher prevalence of pneumonia in this dataset.[18]

Limitations

Despite the large number of datasets available, we were able to validate only four of the eight prediction rules plus both guidelines. The methodological challenges encountered in performing these retrospective validations in prospectively collected datasets limit the translation into clinical practice. Performance of prediction rules was generally lower than in their original derivation studies. Clinical prediction rules tend to perform worse when validated in a new setting.[29] Often clinical prediction rules are only internally validated through split-sample or cross-validation, simply assessing the precision of a clinical prediction rule within its derivation sample. Naturally, this leads to an optimistic estimate of performance.[30] Another possible explanation for this is the approximations that we used for variables measured and recorded in different ways (and different languages).

To avoid potential bias from validating in datasets with missing variables, a sensitivity analyses was performed and, if findings were robust throughout the different datasets, validation was deemed suitable.

In addition to variation in recorded variables, multiple other sources of heterogeneity were found in the included databases, including differences in setting, inclusion criteria, immunization schedules, and definition of serious infection.

Strengths

Although the limitations may be substantial, this is the first study to externally validate existing clinical prediction rules in different types of clinical settings. We used individual patient data from a total of seven existing datasets comprising 11023 children presenting to PC or EDs in three European countries to validate existing prediction rules and national evidence-based guidelines. Previously, only a single prediction rule had been prospectively validated in external datasets.[11-14] Our study therefore presents the first robust attempt to simultaneously validate multiple current prediction rules and evidence-based guidelines for management of one of the most common clinical conditions in AC settings. We anticipate that our findings will be applicable to guideline developers worldwide.

Comparison with other studies

The YOS was initially developed to identify serious illness in febrile children aged 3 to 36 months, but was subsequently discarded based on three prospective validation studies (of which only one was carried out in the intended age group).[11, 13, 14] The rule was also used to stratify patients in five studies evaluating inflammatory markers (such as procalcitonin and C-reactive protein), with discouraging results.[31-35] Bang et al. reported a slightly better performance of the YOS in predicting bacteraemia in febrile children in an HP study (28%), which does not apply to most AC settings.[12] Although the YOS was not useful for ruling out a serious infection in our analysis, a score of greater than 10 (with a combination of the presence of abnormal colour or hydration status, failure to respond to parents, different cry, and abnormal sleepiness) did slightly increase the likelihood of a serious infection in these datasets.

Clinical implications

With decreasing incidence of serious infections, clinicians will increasingly rely on clinical prediction rules in practice, particularly in high-volume triage settings. In these settings, ‘generic’ rules, which apply to all serious infections, are more useful than disease-specific rules. Particularly in settings where diagnosis of serious illness in children is essential (for example, PC), the 4-sDT, the NICE guidelines, and the NHG alarm symptoms may be used to rule out serious infections in a large proportion of children.

We suggest that the 4-sDT, mainly consisting of the child's breathing status and temperature and the clinician's gut feeling that something is wrong, should be used for assessment of every acutely ill child. The meningitis rule, with absence of nuchal rigidity, petechial rash, and coma, indicate that meningitis is highly unlikely in LP settings.
Clinicians should be aware that none of the clinical prediction rules provide perfect discrimination, and it is perhaps unrealistic to expect such rules to provide this. Residual uncertainty may be further improved by conducting more detailed clinical assessments, repeating the assessment after some time, using additional testing (for example, urine or blood tests), and in most cases, providing an appropriate safety netting advice for children sent home detailing instructions on when to seek further care.[36]

Research implications
Most clinical prediction rules never undergo further validation or are implemented, perhaps inappropriately, with insufficient external validation.[37, 38] Indeed very few clinical prediction rules for the identification of children with serious infection have undergone either extensive validation or formal impact analysis, limiting the ability to truly evaluate their performance and to balance benefits and harms.[9, 39] In general, clinical prediction rules perform worse when validated in new populations.[29]

Our study presents the first multiple external validation of clinical prediction rules in this common clinical area, and identifies which of them offer the best diagnostic accuracy in different types of clinical settings. This illustrates the clear need to perform extensive prospective validation and impact analysis of clinical prediction rules prior to clinical implementation.[39, 40] The 4-sDT and the NICE guidelines for assessment of feverish children are potential candidates for future prospective validation studies examining their performance in new prospectively collected data on similar populations.

We recognize the previously identified major mismatch,[3] between the clinical settings where the majority of children with acute infections seek help (that is, PC), and the number of studies performed in that setting (two studies) (**Table 1.3**). There is a pressing need for more studies conducted in PC or in LP ED settings to validate clinical prediction rules for serious infection, or the need for hospital referral/admission. Given the relative infrequency of serious infections, such studies need to include large cohorts of children.[7, 8]

Clinical prediction rules are mostly designed to rule out serious infections, often at the expense of moderate to low ability for inclusion.

As no rule is perfect at ruling out infection, research on the most effective content and methods of delivery with appropriate safety netting advice in PC and EDs is essential.[8, 36, 41] Adding newer tests such as point-of-care inflammatory markers may improve the diagnostic value of these rules, but the performance of these markers in non-referred populations has to be tested.[42]

CONCLUSIONS

None of the clinical prediction rules examined in this study provided adequate diagnostic accuracy. In LP settings (for example, PC) or IP settings, prediction rules, such as the 4-sDT and evidence-based guidelines (NICE guideline and the NHG alarm symptoms) had high sensitivity, providing promising rule-out value for serious infections in these datasets, although all seemed to leave residual uncertainty. Additional clinical assessment or testing such as point-of-care inflammatory markers may be needed to increase clinical certainty. None of the prediction rules identified seemed to be valuable for HP settings (for example, EDs).

ACKNOWLEDGEMENTS

This paper was written on behalf of the European Research Network on Recognising Serious Infection (ERNIE). This study was financially supported by the Health Technology Assessment Project 07/37/05, the National Institute for Health Research under its Programme Grants for Applied Research funding scheme (RP-PG-0407-10347), and the Research Foundation - Flanders (FWO). We would like to thank Dr Nigel Coad, University Hospitals Coventry and the Warwickshire NHS Trust, the staff and parents of Ward B5, Walsgrave Hospital, for their contribution to the study and data by Thompson and colleagues; the WellChild Charity who funded the initial collection of the data, and Professor Terence Stephenson, Professor Jacqueline Collier, and Dr Samiran Ray for their contributions to the initial data collection by Brent and colleagues; the Diagnostic Research in Paediatrics, Health Care Insurance Council of the Netherlands (Zon MW), OG97-041, for funding the initial collection of the data by Oostenbrink and the European Society of Paediatric Infectious Diseases for funding the work of Oostenbrink; the Manchester Triage System, Health Care Insurance Council of the Netherlands (Zon MW) 945-06-211, for funding the initial collection of the data by Moll; The Diagnostic Research in Paediatrics, Health Care Insurance Council of the Netherlands (Zon MW), OG97-041, for funding the initial collection of the data by Bleeker; and (ZonMW), 4200.0012 for funding the initial collection of the data by Berger.

Chapter 1: Appendix.

Comparison with other studies:

The NICE “traffic” light clinical decision tool: a frontline triage system across different health settings.

Published as:

Jan Y Verbakel, Frank Buntinx, Matthew Thompson. A frontline triage system across different health settings. ***BMJ 2013; 346:f2313.***

"TRAFFIC LIGHT" CLINICAL DECISION TOOL: A FRONTLINE TRIAGE SYSTEM ACROSS DIFFERENT HEALTH SETTINGS.

De and colleagues present the validation results of the National Institute for Health and Care Excellence (NICE) "traffic light" system to detect serious bacterial infections in young children with fever.[43] Such research is welcome, because timely recognition of the small number of children with serious bacterial infections among the majority with self-limiting infections is difficult and consumes considerable frontline healthcare resources.[44]

We recently examined the diagnostic accuracy of several clinical prediction rules, including the NICE traffic light system with any amber or red feature present, in ambulatory care: two low prevalence (primary care) and five intermediate to high prevalence (emergency department) datasets from three different countries.[45] Similar to De and colleagues, we found moderate sensitivity for the high prevalence settings (87.1%, 95% CI 82.5 to 90.9).[18]

However, sensitivity was much higher in the low to intermediate prevalence settings, with all sensitivities above 97.3%, suggesting a role in ruling out serious infections. We excluded datasets with a third or more of the required variables missing. In De and colleagues' study, 11 of the 43 NICE traffic light variables were missing and 19 symptoms were used as approximations for other NICE traffic light items, which might explain the differences in accuracy. In addition, De and colleagues' study included fewer meningitis cases, which limited the precision of their findings.

It could be argued that including children with fever ≥38°C might decrease sensitivity, because such a temperature in children under 3 months is considered a red traffic light. However, three of the four datasets that we used included children with fever but had no effect on the results. The unrestricted age range might also have limited our results.

However, a sensitivity analysis that compared the confidence intervals of the diagnostic characteristics for children less than 5 years of age with those for all children found no discrepancies.

Finally, De and colleagues noted that 77% of the data on urine analysis were missing. Furthermore, urinalysis was more common in children who were triaged in category one or two by the Australasian triage scale. Unsurprisingly, this increased sensitivity when added to the NICE traffic light system.

Further research is probably needed before urine analysis becomes part of the diagnostic triage of acutely ill children. Because urine analysis is the first step in managing children with fever of unknown source, its importance cannot be denied.

However, the low specificity and number of false positives raises concerns and might reduce the NICE traffic light system, with or without urine analysis, to its initial intended use - a frontline triage system across different care settings.

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Chapter 2.

Research question

How well do clinical signs, and their prediction rules perform in identifying sepsis and meningitis in acutely ill children admitted to hospital?

Published as:

Jan Y Verbakel, Roderick MacFaul, Bert Aertgeerts, Frank Buntinx, Matthew Thompson. Sepsis and meningitis in Hospitalized Children. ***Pediatr Emerg Care 2014; 30:373-80.***

RETROSPECTIVE VALIDATION OF HOSPITAL-BASED CLINICAL PREDICTION RULES AND VITAL SIGNS TO DETECT SEPSIS AND MENINGITIS IN CHILDREN ADMITTED TO HOSPITAL .

ABSTRACT

Objective: Feverish illness is a common presentation to acute paediatric services. Clinical staff faces the challenge of differentiating the few children with meningitis or sepsis from the majority with self-limiting illness. We aimed to determine the diagnostic value of clinical features and their prediction rules for identifying children with sepsis or meningitis among those children admitted to a District General Hospital with acute febrile illness.

Methods: Acutely ill children admitted to a District General Hospital in England were included in this case-control study between 2000 and 2005. We examined the diagnostic accuracy of individual clinical signs and 6 clinical prediction rules, of which the modified Yale Observation Scale and AVPU scale were scored prospectively at the time of admission and the other four were examined retrospectively, to determine clinical utility in identifying children with a diagnosis of sepsis or meningitis.

Results: Loss of consciousness, prolonged capillary refill, decreased alertness, respiratory effort, and the physician's illness assessment had high positive likelihood ratios (9-114), although with wide confidence intervals, to rule in sepsis or meningitis. The National Institute for Clinical Excellence traffic light system, the modified Yale Observation Scale, and the Paediatric Advanced Warning Score performed poorly with positive likelihood ratios ranging from 1 to 3.

Conclusions: The paediatrician's overall illness assessment was the most useful feature to rule in sepsis or meningitis in these acutely ill children admitted to hospital. Clinical prediction rules did not effectively rule in sepsis or meningitis. The modified Yale Observation Scale should be used with caution. Single clinical signs could complement these scores to rule in sepsis or meningitis. Further research is needed to validate these clinical prediction rules.

BACKGROUND

Feverish illness, usually caused by infection, is one of the most common presentations of children to health care services.[1] In the United Kingdom, infections are a significant cause of childhood deaths (of which >26% are judged to be avoidable), especially in the age group of 1 to 4 years.[1] Most children presenting with febrile illness have self-limiting infections, but 50% of admissions to hospital are associated with infection, and up to 30% of febrile children presenting to hospital have a serious infection.[2] The challenge faced by paediatricians is the need to identify the few children with serious bacterial infections (SBIs), such as bacterial meningitis, bacteraemia, and sepsis.
The previously reported red flags for SBI in hospitalized children include toxic appearance; abnormal vital signs such as temperature and capillary refill time (CRT), and raised inflammatory markers.[3-5] However, the evidence base underlying many clinical features is limited because most studies have been small and based in tertiary hospitals where disease prevalence, case mix, clinical staffing, and diagnostic facilities differ markedly from District General Hospitals (DGHs). Because approximately 75% of all acute paediatric admissions in the United Kingdom involve care in DGH rather than tertiary academic centres, there is a major gap in the evidence to support assessment of acutely ill children in such settings.

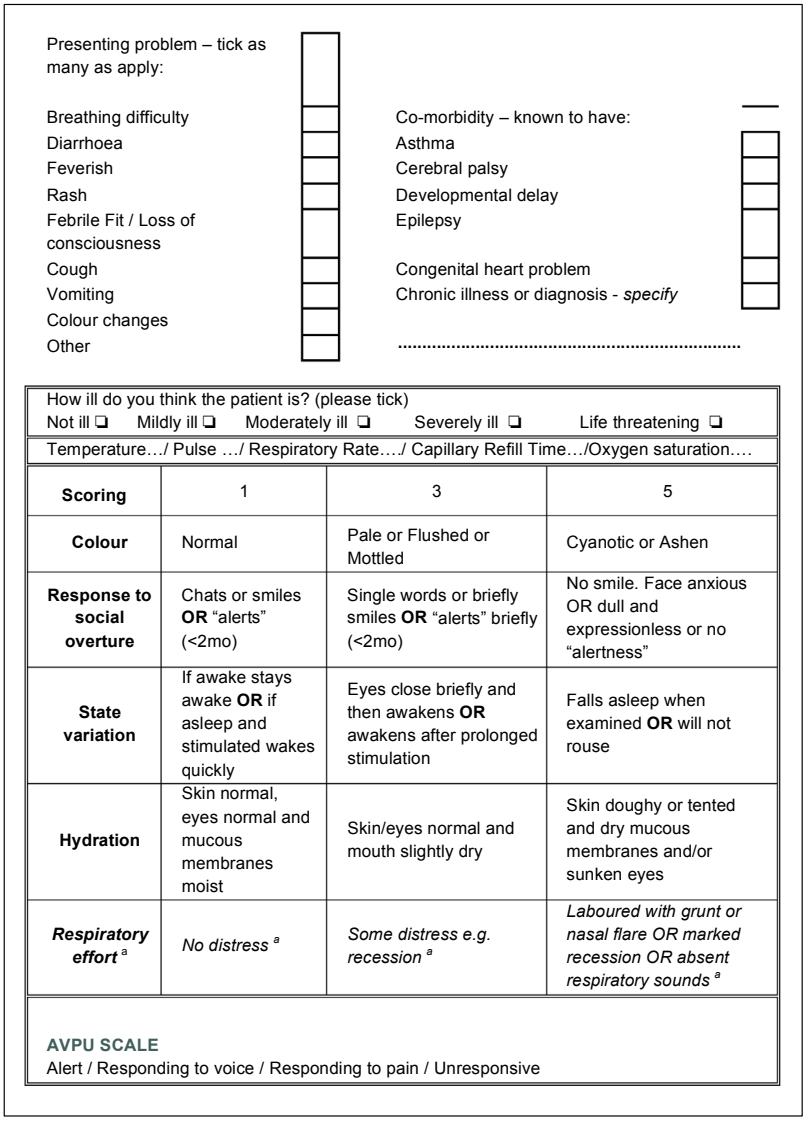
We therefore aimed to determine the diagnostic value of clinical features and clinical prediction rules for identifying children with sepsis or meningitis at the time of admission to a DGH with acute febrile illness.

METHODS

We identified all children, up to 16 years, hospitalized at Pinderfields Hospital (Wakefield, United Kingdom) between 2000 and 2005 after referral by a general practitioner or self-referred attendance at the emergency department in this case-control study. Pinderfields Hospital has 40 children's beds serving a local population of approximately 200000 children and an admission rate of 80 per 1000 (national rate, 89 per 1000 child population per year).[6]

On admission, each child underwent a structured clinical assessment by the admitting paediatrician, which included vital signs (temperature, heart and respiratory rates, CRT, and oxygen saturation (S_pO_2)), an overall assessment of ''how ill does this child appear?", a scale evaluating the child's response to Alert, Voice, Pain, or Unresponsive (AVPU),[7] and clinical assessment of a modified version of the Yale Observation Scale (YOS; **Figure 2.1**).[8, 9]

Most children in our study underwent additional tests (full blood count, C-reactive protein, blood and urine culture, lumbar puncture, and chest X-ray) according to a standardized protocol. A consultant paediatrician recorded the final discharge diagnosis on a database with full knowledge of the clinical findings and laboratory and imaging results.



Presenting problem – tick as many as apply:

- Breathing difficulty ☐
- Diarrhoea ☐
- Feverish ☐
- Rash ☐
- Febrile Fit / Loss of consciousness ☐
- Cough ☐
- Vomiting ☐
- Colour changes ☐
- Other ☐

Co-morbidity – known to have:

- Asthma ☐
- Cerebral palsy ☐
- Developmental delay ☐
- Epilepsy ☐
- Congenital heart problem ☐
- Chronic illness or diagnosis - *specify* ☐

.....

How ill do you think the patient is? (please tick)
Not ill ❑ Mildly ill ❑ Moderately ill ❑ Severely ill ❑ Life threatening ❑

Temperature…/ Pulse …/ Respiratory Rate…./ Capillary Refill Time…/Oxygen saturation….

Scoring	1	3	5
Colour	Normal	Pale or Flushed or Mottled	Cyanotic or Ashen
Response to social overture	Chats or smiles **OR** "alerts" (<2mo)	Single words or briefly smiles **OR** "alerts" briefly (<2mo)	No smile. Face anxious OR dull and expressionless or no "alertness"
State variation	If awake stays awake **OR** if asleep and stimulated wakes quickly	Eyes close briefly and then awakens **OR** awakens after prolonged stimulation	Falls asleep when examined **OR** will not rouse
Hydration	Skin normal, eyes normal and mucous membranes moist	Skin/eyes normal and mouth slightly dry	Skin doughy or tented and dry mucous membranes and/or sunken eyes
Respiratory effort [a]	*No distress* [a]	*Some distress e.g. recession* [a]	*Laboured with grunt or nasal flare OR marked recession OR absent respiratory sounds* [a]

AVPU SCALE
Alert / Responding to voice / Responding to pain / Unresponsive

Figure 2.1: Admission sheet (with the modified YOS) of the Pinderfields Paediatric Department.

[a]Nelson modification of the YOS (the item ''respiratory effort'' replaces the original Yale item ''quality of cry'').

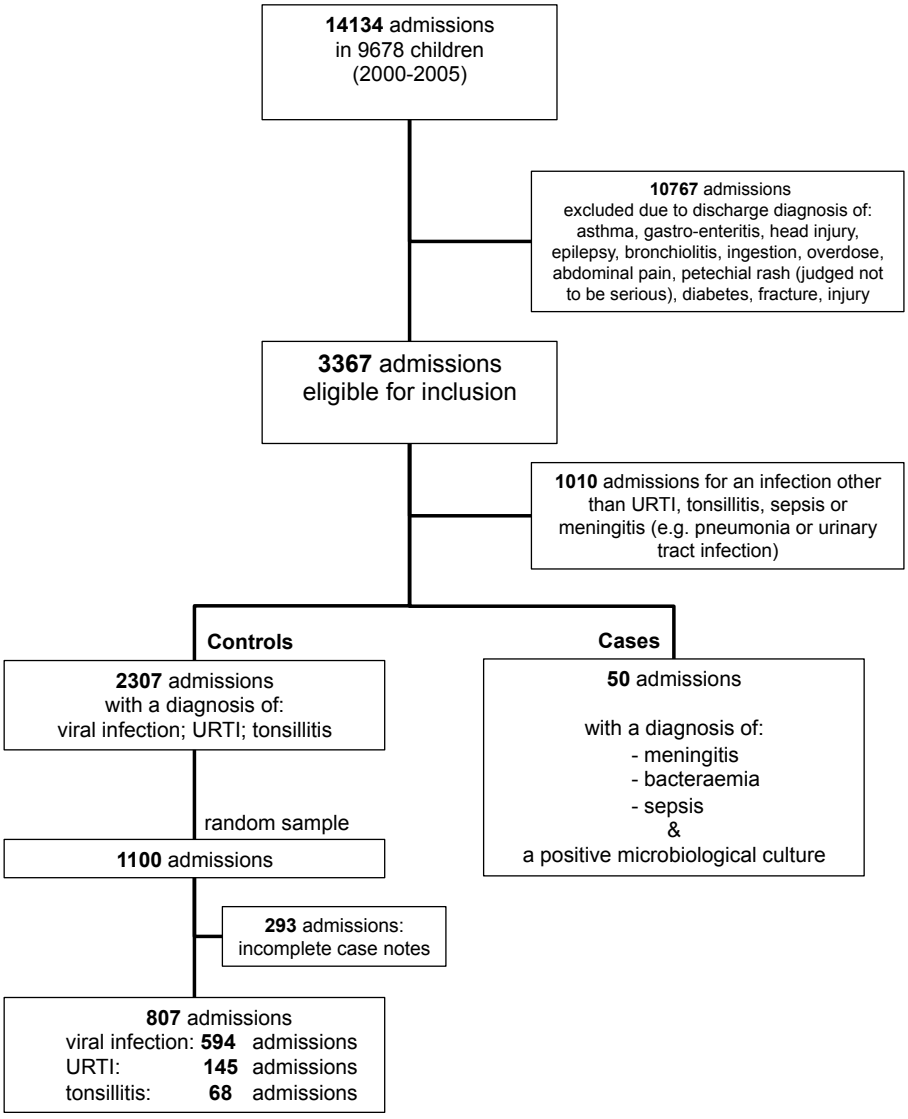


Figure 2.2: Ascertainment of cases and controls
URTI: upper respiratory tract infections

Two research assistants extracted the data from the case records. We identified all children with a discharge diagnosis of bacterial meningitis, bacteraemia, or sepsis, with pathogenic bacteria isolated from a normally sterile site (cerebrospinal fluid or blood culture). A control group consisted of a half random sample of all children (using Microsoft Excel's random sample feature), with a final diagnosis of a self-limiting or mild infection, including tonsillitis, viral or upper respiratory tract infections, with negative sterile site microbiologic cultures.

Children were excluded if their clinical features clearly pointed to an alternative diagnosis, according to a consultant paediatrician's review of the database, e.g. gastroenteritis, head injury or epilepsy (**Figure 2.2**).
In accordance with the current NICE guidelines for feverish illness in children,[10] the following cut-offs were used: temperature (≥38.0°C), S_pO_2 (≤95%), and CRT (≥3 seconds), as well as additional cut-offs for temperature (≥39.0°C) and S_pO_2 (<98%), based on clinical consensus. The Advanced Paediatric Life Support (APLS)[11] cut-offs were used for heart and respiratory rate, in addition to heart rate centiles adjusted for temperature and age.[12]

Clinical Prediction Rules
Six clinical prediction rules (first 2 scored prospectively on admission, 4 others examined retrospectively) were selected for the analysis:

1. a modified YOS providing a sum score, with an abnormal result defined using 2 preselected cut-offs (>8 or 10; **Figure 2.1**)[1, 8]
2. the AVPU scale (**Figure 2.1**)
3. the Paediatric Advanced Warning Score (PAWS) using the red scores for temperature, heart and respiratory rate, S_pO_2, respiratory effort, the AVPU scale, and CRT[13]
4. a score developed by the UK's Royal College of Paediatrics and Child Health Recognising Acute Illness in Children working group on (RAIC score) scoring 8 clinical variables (developmental delay, risk factor for infection, state variation, temperature, CRT, hydration status, respiratory rate, and hypoxia).[14] The score was dichotomized in 2 ways (≥8 designed to rule in and ≤5 to rule out sepsis or meningitis).
5. the Oxford Vital Signs score consisting of the presence of 1 or more abnormal vital signs (temperature, ≥39.0°C; S_pO_2 ≤94%; tachycardia; and tachypnoea)[15]
6. the NICE febrile illness guideline ''traffic light system,'' with either any red or any amber or red traffic light present (**Table 2.1**).[10]

The diagnostic accuracy of clinical signs and clinical prediction rules was assessed by calculating sensitivity, specificity, and likelihood ratios with 95% confidence intervals (CIs) for sepsis or meningitis.
Symptoms or prediction rules were considered clinically useful at ruling in if, when positive, they substantially raised the probability of SBI, (positive likelihood ratio (LR+) > 5.0) and conversely good at ruling out SBI if, when negative, they substantially lowered the probability of SBI (negative likelihood ratio (LR-) < 0.2).[16] For example, at a prevalence of 5%, a LR+ of 5 or a LR- of 0.2 would result in a post-test probability of 21% and 1%, respectively. When a rule was specifically designed for a certain age group (e.g., the YOS for children 3-36 months and the NICE guidelines for children up to 5 y), we visually compared the 95% CIs of their diagnostic characteristics (sensitivity, specificity, LR+, LR-).

Table 2.1: Details of the clinical prediction rules

Name of Clinical severity score	Clinical features								Derivation study
Paediatric Advanced Warning Score (PAWS)	temperature	heart rate	respiratory rate	O_2 saturation	respiratory effort	AVPU scale	CRT		Egdell et al. 2008[13]
Red scores	< 36°C	0-1 yr: ≤ 100/min *or* > 170/min 1-3 yrs: ≤ 80/min *or* > 170/min 3-5 yrs: ≤ 70/min *or* > 155/min 5-12 yrs: ≤ 55/min *or* > 140/min > 12 yrs: ≤ 50/min *or* > 120/min	0-1 yr: ≤ 18/min *or* > 60/min 1-3 yrs: ≤ 14/min *or* > 48/min 3-5 yrs: ≤ 12/min *or* > 46/min 5-12 yrs: ≤ 10/min *or* > 36/min > 12 yrs: ≤ 8/min *or* > 30/min	< 80%	Signs of respiratory distress *or* poor respiratory effort	Response to painful stimuli *or* unresponsive	> 3 seconds	
Values	If yes to any of these seven categories, each scoring 1 or 2 features								
Recognising Acute Illness in Children score (RAIC)	developmental delay	risk factor for infection	state variation	temperature	CRT	hydration status	respiratory rate	hypoxia	Brent et al. 2011[14]
Values	No delay 0 Delay 4	No risk factor 0 Risk factor 2	Eyes open 0 Eyes close briefly 1 Falls asleep 2	< 37.5°C 0 37.5°C-38.4°C 1 >38.5°C 2	< 2 seconds 0 ≥ 2 seconds 1	Well hydrated 0 Dry mucous membranes 2 Reduced skin turgor 4	Not tachypnoeic 0 Tachypnoeic 1	Not hypoxic 0 Mild hypoxia 1 Severe hypoxia 2	
	Calculate the sum of all eight feature values (cut-offs used: ≥ 8 rule in sepsis or meningitis; ≤ 5 to rule out sepsis/meningitis)								
Oxford Vital Signs Score	temperature ≥ 39°C	S_pO_2 ≤ 94%		tachycardia	tachypnoea				Thompson et al. 2009[15]
Values	If yes to any of these four features								
NICE traffic light system	colour	activity	respiratory	hydration	other				NICE: Feverish Illness in Children[10]
Amber traffic lights	- pallor	- not responding to social cues - wakes only with prolonged stimulation - decreased activity - no smile	- nasal flaring - tachypnoea (age 6-12 months: RR >50/min; age >12 months: > 40/min) - O_2 saturation ≤ 95% - crackles	- dry mucous membranes - poor feeding in infants - CRT ≥ 3 seconds - reduced urine output	- fever for temp ≥5 days - swelling of a limb or joint - non-weightbearing limb/not using extremity - a new lump >2 cm				
Red traffic lights	- pale/mottled/ ashen/blue	- no response to social cues - appears ill to doctor - does not wake or if roused does not stay awake - weak high-pitched or continuous cry	- grunting - tachypnoea (>60/min) - moderate/severe chest indrawing	- reduced skin turgor	- age 0-3 months, temp ≥38°C - age 3-6 months, temp ≥39°C - non-blanching rash - bulging fontanel - neck stiffness - status epilepticus - focal neurological signs - focal seizures - bile-stained vomiting				
Values	If yes to any of these 5 categories, each scoring 2 to 13 features								

RR: respiratory rate; sepsis or meningitis: bacterial meningitis/bacteraemia/sepsis; temp: temperature

RESULTS

From August 2000 to July 2005, there were 14699 admissions in 9678 children (average of 1.52 admissions per child). We excluded 10767 children from the analysis, with symptoms clearly pointing to alternative diagnoses (**Figure 2.2**).

We included all 50 children with a discharge diagnosis of bacterial meningitis, bacteraemia, or sepsis and a positive sterile site culture. The most frequent bacterial isolates were Streptococcus pneumoniae and Neisseria meningitidis (**Table 2.2**)

Table 2.2: Causative pathogens of included meningitis/bacteraemia/sepsis cases

Diagnosis	n	Neisseria meningitidis	Streptococcus pneumoniae	Haemophilus influenzae	Coagulase-negative Staphylococcus	Alpha haemolytic Streptococcus	Beta haemolytic Streptococcus	Escherrichia coli
meningitis	**18**	0	13	0	1	1	1	2
bacteraemia	**16**	4	6	3	2	0	1	0
sepsis	**16**	7	6	1	0	2	0	0
total	**50**	11	25	4	3	3	2	2

n. number of cases

Out of 2307 children admitted over the study period with a discharge diagnosis of tonsillitis, upper respiratory tract infection, and other viral infection, we identified a random sample of 1100 children and obtained full data from 807 children.

Of a total of 50 children with sepsis or meningitis, there were 27 boys and 23 girls (age, both ranging from 0 to 15 years; **Table 2.3**). The median age was not statistically significantly different between the group with sepsis or meningitis (15 months) and the control group (23 months) (p=0.006).

Table 2.3: Baseline characteristics of included children

Characteristics	Cases (n=50)	Controls (n=807)
	meningitis/ bacteraemia/ sepsis (n=50)	tonsillitis, upper respiratory tract and other viral infection (n=807)
Gender, n (%)		
male	27 (54.0)	453 (56.1)
female	23 (46.0)	353 (43.7)
Age, n (%)		
<1 month	1 (2.0)	23 (2.9)
1-12 months	18 (36.0)	213 (26.4)
13-36 months	23 (46.0)	271 (33.6)
37-60 months	3 (6.0)	114 (14.1)
61-144 months	4 (8.0)	162 (20.1)
>145 months	1 (2.0)	24 (3.0)
Age median (IQR) in months	15.3 (8.0-24.1)	23.3 (10.2-56.8)

n. number of cases; IQR. interquartile range

Some individual symptoms (febrile fit or loss of consciousness), the clinician's overall assessment of illness, and CRT greater than or equal to 3 seconds had high LR+ for sepsis or meningitis (LR+, 8.7 (95% CI, 4.6 to 16.4) to 89.5 (95% CI 16.2 to 495)) although with wide CIs (**Figure 2.3**) at sensitivities below 25% and specificities above 97%.

A temperature of greater than or equal to 39°C, respiratory rate or heart rate exceeding the APLS cut-offs, heart rate-temperature centile above the 95th centile, and S_pO_2 of less than 95% all had more modest LR+, ranging between 1.1 (95% CI 1.0 to 1.2) and 3.8 (95% CI 1.3 to 10.7) with sensitivities below 70% and specificities ranging from 68 to 98%.

A YOS score of above 8 resulted in a LR+ of 1.0 (95% CI 0.9 to 1.0) for sepsis or meningitis with a sensitivity of 98% (95% CI 89-100%), however at a specificity of 2% (95% CI 1-4%). Several individual features from the YOS (''state variation'' (decreased alertness) and ''respiratory effort'') when scored as highly abnormal (score of 5) had a LR+ ranging from 16.7 (95% CI 2.4 to 116.0) to 114.0 (95% CI 5.97 to 2174.0), again with wide CIs (**Figure 2.3**), and all specificities ranging from 73 to 100% at sensitivities all below 57%.

The PAWS had a moderate LR+ (3.1) and LR- (0.5) at a sensitivity of 58% (95% CI 43-72%) and a specificity of 81% (95% CI 78-84%). Both the AVPU scale (child responding only to pain stimuli or being unresponsive) and the RAIC score (≥8) had high LR+ of 83.2 to 284.0 although with very wide CI for sepsis or meningitis with 100% specificity, however at sensitivities below 18%, and the Oxford Vital Signs score (with a sensitivity of 80%) had the lowest LR- of 0.4 (95% CI 0.2 to 0.7) at a specificity of 49% (95% CI 46-53%).

We were able to validate 9 (pallor, response to social cues, wakes with prolonged stimulation, decreased activity, no smile, nasal flaring, tachypnoea, oxygen saturation, dry mucous membranes, and CRT) of the 17 ambers, and 11 (ashen colour, no response to social cues, appears ill, does not wake, grunting, tachypnoea, chest indrawing, reduced skin turgor, focal seizures, temperature, and age) of the 18 red NICE febrile illness traffic light features. The presence of any of the 7 ambers or 11 red signs provided a sensitivity of 100% (95% CI 93 to 100%) and specificity of only 0.1% (95% CI 0.0-0.7%) at a LR+ of 1.00 (95% CI 0.97 to 1.02). (**Figure 2.3**)

Comparing the 95% CIs, we found similar results for the diagnostic characteristics of the YOS and the NICE guidelines in children of all ages as well as in children for whom the rules were originally designed (3 to 36 months and up to 5 y, respectively) (**Table 2.4**).

item	fn/N[a]	sensitivity (95% CI)	specificity (95% CI)	likelihood ratio (95% CI) negative	likelihood ratio (95% CI) positive
Symptoms					
breathing difficulty	49/857	2.00 (0.05-10.6)	98.8 (97.7-99.4)	0.99 (0.9-1.03)	1.61 (0.21-12.4)
fever	29/857	42.0 (28.2-56.8)	89.3 (87.0-91.4)	0.65 (0.51-0.82)	3.94 (2.69-5.78)
diarrhoea	48/857	4.00 (0.49-13.7)	98.9 (97.9-99.5)	0.97 (0.92-1.03)	3.59 (0.80-16.2)
febrile fit or loss of consciousness	45/857	10.0 (3.30-21.8)	99.6 (98.9-99.9)	0.90 (0.82-0.99)	26.9 (6.62-109)
how ill does child appear?	39/804	17.0 (7.65-30.8)	99.9 (99.3-100)	0.83 (0.72-0.94)	89.5 (16.2-495)
Vital signs					
temperature					
≥38°C	17/855	66.0 (51.2-78.8)	62.5 (59.0-65.8)	0.54 (0.37-0.80)	1.76 (1.41-2.19)
≥39°C	35/855	30.0 (17.9-44.6)	88.8 (86.4-90.9)	0.79 (0.66-0.95)	2.68 (1.68-4.28)
respiratory rate					
exceeds APLS cut-offs for age	36/839	28.0 (16.2-42.5)	76.0 (72.9-79.0)	0.95 (0.79-1.13)	1.17 (0.74-1.85)
heart rate					
exceeds APLS cut-offs for age	15/849	70.0 (55.4-82.1)	68.3 (65.0-71.6)	0.44 (0.29-0.67)	2.21 (1.80-2.72)
exceeds heartrate-temperature 90th percentile for age	44/847	12.0 (4.53-24.3)	93.7 (91.8-95.3)	0.94 (0.85-1.04)	1.91 (0.86-4.24)
exceeds heartrate-temperature 95th percentile for age	46/847	8.00 (2.22-19.2)	97.9 (96.6-98.8)	0.94 (0.87-1.02)	3.75 (1.31-10.7)
oxygen saturation					
less than 95%	33/509	13.2 (4.41-28.1)	80.5 (76.6-84.0)	0.67 (0.29-1.56)	1.08 (0.95-1.23)
less than 98%	14/509	63.2 (46.0-78.2)	21.4 (17.8-25.4)	0.80 (0.63-1.03)	1.72 (1.09-2.7)
capillary refill					
≥ 3 seconds	36/810	25.0 (13.6-39.6)	97.1 (95.7-98.2)	0.77 (0.66-0.91)	8.66 (4.57-16.4)
Clinical prediction rules					
Yale Observation Scale					
Yale colour = 5	20/829	56.5 (41.1-71.1)	72.9 (69.7-76.0)	0.60 (0.43-0.83)	2.09 (1.58-2.76)
Yale response to social overtures = 5	26/829	35.0 (20.6-51.7)	82.5 (79.7-85.1)	0.79 (0.63-0.99)	2.00 (1.28-3.13)
Yale state variation = 5	44/827	6.38 (1.34-17.5)	100 (99.5-100)	0.93 (0.86-1.00)	114 (5.97-2174)
Yale hydration = 5	38/851	24.0 (13.1-38.2)	91.0 (88.8-92.9)	0.84 (0.71-0.98)	2.67 (1.56-4.58)
Yale respiratory = 5	45/831	4.26 (0.52-14.5)	99.7 (99.1-100)	0.96 (0.90-1.02)	16.7 (2.4-116)
Yale Observation Scale > 8	1/857	98.0 (89.4-99.9)	2.35 (1.42-3.65)	0.85 (0.12-6.55)	1.00 (0.96-1.05)
Yale Observation Scale > 10	23/857	54.0 (39.3-68.2)	63.7 (60.3-67.0)	0.72 (0.53-0.98)	1.49 (1.13-1.95)
NICE traffic light system					
if any amber or red sign present	0/857	100 (92.9-100)	0.12 (0.00-0.69)	5.28 (0.22-128)	0.99 (0.97-1.02)
if any red sign present	19/857	62.0 (47.2-75.3)	74.5 (71.3-77.4)	0.51 (0.36-0.73)	2.43 (1.90-3.11)
Paediatric Advanced Warning Score					
if any red sign was present according to PAWS	21/857	58.0 (43.2-71.8)	81.3 (78.4-83.9)	0.52 (0.37-0.72)	3.10 (2.35-4.09)
AVPU scale					
if child response to pain (P) stimulus	37/813	17.8 (8.00-32.1)	100 (99.5-100)	0.82 (0.71-0.94)	284 (16.7-4848)
RAIC Score[b]					
RCPCH RAIC score ≥8 (rule in SBI)	48/857	4.00 (0.49-13.7)	100 (99.5-100)	0.95 (0.89-1.01)	83.2 (3.94-1758)
RCPCH RAIC score ≤5 (rule out SBI)	12/827	76.0 (61.8-86.9)	6.20 (4.63-8.09)	0.81 (0.69-0.95)	3.87 (2.21-6.79)
Oxford Vital Signs Score[c]					
if yes to any of [d]	10/857	80.0 (66.3-90.0)	49.3 (45.8-52.8)	0.41 (0.23-0.71)	1.58 (1.35-1.84)

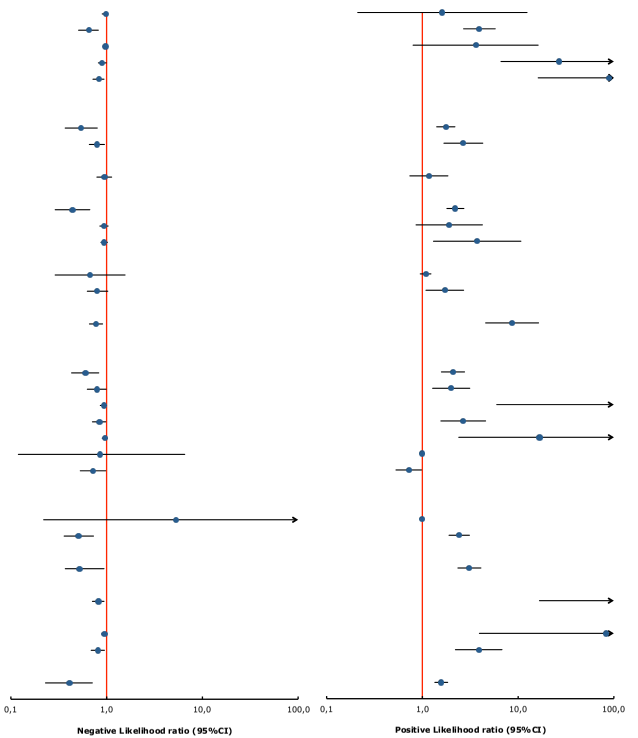


Figure 2.3: Results of clinical features in predicting meningitis, bacteraemia or sepsis

[a]Number of false negative out of all children; [b]RAIC score: risk score developed by the Royal College of Paediatrics and Child Health working group on Recognising Acute Illness in Children, London, United Kingdom; [c]Oxford Vital Signs Score: vital signs severity score developed by the Department of Primary Care Health Sciences, Centre for Monitoring and Diagnosis in Primary Care, Oxford, United Kingdom; [d]Temperature ≥ 39°C, S_pO_2 ≤ 94%, tachycardia (according to the APLS cut-offs), tachypnoea (according to the APLS cut-offs).

Table 2.4: Sensitivity analysis for age range of the modified Yale Observation Scale and the NICE traffic light system

clinical prediction rule	conditions	% sensitivity (95% CI)	% specificity (95% CI)	Likelihoodratio (95% CI) positive	negative
Yale Observation Scale					
Yale colour = 5	all ages	56.5 (41.1-71.1)	72.9 (69.7-76.0)	0.60 (0.43-0.83)	2.09 (1.58-2.76)
	limited to age range 3 to 36 months	57.7 (40.9-73.0)	74.9 (70.9-78.7)	0.57 (0.39-0.82)	2.3 (1.69-3.12)
Yale response to social overtures = 5	all ages	35.0 (20.6-51.7)	82.5 (79.7-85.1)	0.79 (0.63-0.99)	2.00 (1.28-3.13)
	limited to age range 3 to 36 months	32.4 (17.4-50.5)	83.2 (79.6-86.4)	0.81 (0.64-1.03)	1.92 (1.14-3.25)
Yale state variation = 5	all ages	6.38 (1.34-17.5)	100 (99.5-100)	0.93 (0.86-1.00)	114 (5.97-2174)
	limited to age range 3 to 36 months	4.88 (0.60-16.5)	100 (99.3-100)	0.94 (0.87-1.02)	58.6 (2.86-1200)
Yale hydration = 5	all ages	24.0 (13.1-38.2)	91.0 (88.8-92.9)	0.84 (0.71-0.98)	2.67 (1.56-4.58)
	limited to age range 3 to 36 months	19.0 (8.60-34.1)	92.4 (89.8-94.6)	0.88 (0.76-1.02)	2.52 (1.26-5.05)
Yale respiratory = 5	all ages	4.26 (0.52-14.5)	99.7 (99.1-100)	0.96 (0.90-1.02)	16.7 (2.4-116)
	limited to age range 3 to 36 months	4.88 (0.60-16.5)	99.6 (98.5-100)	0.96 (0.89-1.02)	12.1 (1.75-83.5)
Yale Observation Scale > 8	all ages	98.0 (89.4-99.9)	2.35 (1.42-3.65)	0.85 (0.12-6.55)	1.00 (0.96-1.05)
	limited to age range 3 to 36 months	97.6 (87.4-99.9)	2.37 (1.23-4.1)	1.01 (0.13-7.55)	1.00 (0.95-1.05)
Yale Observation Scale > 10	all ages	54.0 (39.3-68.2)	63.7 (60.3-67.0)	0.72 (0.53-0.98)	1.49 (1.13-1.95)
	limited to age range 3 to 36 months	54.8 (38.7-70.2)	63.9 (59.6-68.1)	0.71 (0.50-0.99)	1.52 (1.13-2.04)
NICE guidelines					
if any amber or red sign present	all ages	100 (92.9-100)	0.12 (0.00-0.69)	5.28 (0.22-128)	0.99 (0.97-1.02)
	limited to age range 0 to 5 years	100 (92.3-100)	0.16 (0.00-0.89)	4.41 (0.18-107)	0.99 (0.96-1.02)
if any red sign present	all ages	62.0 (47.2-75.3)	74.5 (71.3-77.4)	0.51 (0.36-0.73)	2.43 (1.90-3.11)
	limited to age range 0 to 5 years	65.2 (49.8-79.6)	72.6 (68.9-76.1)	0.48 (0.32-0.71)	2.38 (1.86-3.05)

95% CI: 95 % confidence intervals

DISCUSSION

The single clinical features, most useful for ruling in sepsis or meningitis in children hospitalized in DGH, were as follows: clinician's overall assessment of severity of illness, decreased alertness (the YOS state variation item), respiratory effort, and loss of consciousness. There was limited evidence to support the use of clinical prediction rules in both ruling in and ruling out sepsis or meningitis in this setting with a probable high prevalence of serious infections. A high RAIC score or a child responding only to pain or being unresponsive on the AVPU score was useful to rule in meningitis, bacteraemia, or sepsis. We found that only the NICE traffic light system was clinically useful in ruling out sepsis or meningitis in febrile children admitted to hospital, with any amber or red signs considered providing sensitivities of 100%.

This is the first study in children admitted to a UK DGH to evaluate clinical appearance and subjective rating of ''how ill'' a child is overall, together with several clinical prediction rules. Our findings are likely to be generalizable to other hospitals in Europe. There was a high rate of data capture during the period of 5 years, a systematic protocol for the management of febrile children, and a high rate of blood investigations and microbiologic cultures.

Our study has a number of potential limitations. First, the selection of children may result in selection bias. However, although sampling within those groups was random, these analyses should be robust.[17]
Since our analysis was performed on anonymized case notes without prior informed consent, we were not able to retrace which proportion of children were admitted more than once and accounted for more than one admission in our analyses. However, diagnoses requiring recurrent admissions, such as asthma, epilepsy, and diabetes were excluded beforehand, reducing the re-admission rate in these children. A case-control design has been shown to be more vulnerable to inflation of diagnostic values. Although it is not always the case, its presence cannot be tested.[18] Although spectrum bias tends to be present in case-control studies, our results are very much comparable with prior research in secondary care.[1, 15]
Second, the measurement of predictors might be inaccurate, although these were done according to normal ward protocols. Third, some of the clinical prediction rules were designed for certain age groups (e.g. the YOS at 3-36 months, the NICE for 0-5 years), settings (e.g. the Oxford Vital Signs score for the paediatric assessment unit, the PAWS for paediatric intensive care unit), and certain purposes (e.g. the Oxford Vital Signs score for SBI) and may not apply to our age range, setting, and outcome.

Finally, our study was performed in the period before immunization against Streptococcus pneumoniae, resulting in higher rates of sepsis or meningitis caused by this pathogen, compared with the post-immunization period. However, this provided a unique opportunity to examine the accuracy of several individual features and prediction rules.

Indeed, more recent and larger studies have had very limited ability to study sepsis and bacterial meningitis because of low numbers.[19]

Although difficult to test in future studies, we do not feel that the subsequent decline in the prevalence of invasive bacterial pathogens reduces the clinical implications of our findings.

Our study confirms the usefulness of a paediatrician's overall illness assessment to rule in sepsis or meningitis, which has been documented in ambulatory care settings.[1] Although demonstrating high sensitivities, the modified YOS, applied without age restrictions, had no value at ruling in or ruling out sepsis or meningitis, which is similar to previous findings.[1, 20] The YOS was derived in a tertiary US hospital in the 1980s and used methods now considered crude to identify and combine predictors.

The NICE traffic light system performed similar as 2 other studies but the same limitations apply, concerning age range and the number of amber or red features, which had simply not been recorded in our database.[15, 20, 21] Thompson et al[15] found similar sensitivities, examining the diagnostic value of vital signs and the NICE traffic light system for identifying children with serious infections in a paediatric assessment unit. In a previous study by Verbakel et al,[20] the NICE traffic light system was highly sensitive in low- and intermediate-prevalence settings, suggesting clinical value for ruling out serious infections in children. De et al found moderate sensitivities for the NICE traffic light system in a high-prevalence setting, however, with very few cases of sepsis and meningitis identified in their dataset.[22]

We were unable to confirm the results of the only published study of the PAWS, demonstrating a sensitivity of 70% and a specificity of 90% in identifying children who needed admission to the intensive care unit.[13] These limitations highlight the need for validation of clinical prediction rules to prepare them for impact analysis, enabling clinicians to evaluate whether a prediction rule will be ''fit for purpose'' or not.[23-25]

An ill-appearing child with breathing difficulty, loss of consciousness, prolonged capillary refill, increased respiratory effort, and decreased alertness constitutes ‘‘red flags’’ for possible sepsis or meningitis in this setting and should prompt additional clinical assessment, monitoring, and where appropriate, laboratory testing. Our study shows that even ‘‘one-off’’ measurements are helpful to rule in or rule out sepsis or meningitis on admission. We did not find one clinical prediction rule that could meet the needs of paediatric staff, but some individual clinical signs could be used.

The paediatric admission rates of acutely ill children in the United Kingdom continue to rise.[26, 27] The impact on resource use can be substantial. This strongly supports the need for well-conducted research on common issues (such as febrile children) to support the evidence base in these settings. In particular, we need to focus on the value of structured sequential observations, refining these features to ensure their ability to rule in or rule out sepsis or meningitis and further validation of clinical prediction rules.

We conclude that a physician’s overall illness assessment could be the most useful feature to rule in sepsis or meningitis in hospitalized children. In contrast, clinical prediction rules, such as the NICE traffic light system, do not effectively rule out sepsis or meningitis in a high-prevalence setting. Single clinical feature could complement these scores to adequately rule in sepsis or meningitis in hospitalized children. However, further research is needed to validate the clinical prediction rules in this setting and their impact on the management of febrile children.

ACKNOWLEDGMENTS

We would like to thank William MacFaul and John Hickman for gathering the initial data. The views expressed in this publication are those of the authors and not necessarily those of the National Health Service, the National Institute for Health Research, or the Department of Health.

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Chapter 3.

Research question

Can we validate a clinical prediction rule based on signs and symptoms in a new but similar population?

Submitted as:

Jan Y Verbakel, Marieke B Lemiengre, Tine De Burghgraeve, An De Sutter, Bert Aertgeerts, Dominique MA Bullens, Bethany Shinkins, Ann Van den Bruel, Frank Buntinx. Validating a decision tree for serious infection in acutely ill children in ambulatory care.

Protocol published as:

Jan Y Verbakel, Marieke B Lemiengre, Tine De Burghgraeve, An De Sutter, Dominique M A Bullens, Bert Aertgeerts, Frank Buntinx, on behalf of the ERNIE 2 collaboration. Diagnosing serious infections in acutely ill children in ambulatory care (ERNIE 2 study protocol part A): diagnostic accuracy of a Clinical Decision Tree and added value of a Point-of-Care C-reactive protein Test. ***BMC Pediatr 2014, 14:207.***

and:

Marieke B Lemiengre, Jan Y Verbakel, Tine De Burghgraeve, Bert Aertgeerts, Frans De Baets, Frank Buntinx, An De Sutter, on behalf of the ERNIE2 collaboration. Optimizing antibiotic prescribing for acutely ill children in primary care (ERNIE2 study protocol, part B): a cluster randomized, factorial controlled trial evaluating the effect of a Point-of-Care C-reactive protein test and a brief intervention combined with written safety net advice. ***BMC Pediatr 2014, 14:246.***

DIAGNOSING SERIOUS INFECTIONS IN ACUTELY ILL CHILDREN IN AMBULATORY CARE: PROSPECTIVE VALIDATION OF A CLINICAL DECISION TREE BASED ON SIGNS AND SYMPTOMS.

ABSTRACT

Background: Acute infection is the most common presentation of children in primary care with only few having a serious infection (e.g. sepsis, meningitis, pneumonia). To avoid complications or death, early recognition and adequate referral are essential. Clinical prediction rules have the potential to improve diagnostic decision making for rare but serious conditions. In this study, we aimed to validate a recently developed decision tree in a new but similar population.

Methods: This is a diagnostic accuracy study validating a clinical prediction rule of clinical features for serious infections. Acutely ill children presenting to a general practitioner or paediatrician were included consecutively in Flanders, Belgium. Physicians were asked to score the 4-step decision tree, in addition to a thorough clinical assessment and their usual care. The outcome of interest was hospital admission for at least 24 hours with a serious infection within 5 days after initial presentation. We report the diagnostic accuracy of the decision tree in sensitivity, specificity, positive and negative likelihood ratios, and positive and negative predictive values.

Results:
In total, 8664 acute illness episodes were available for analysis of which 283 lead to admission to hospital with a serious infection. Sensitivity of the decision tree was 100% (95% CI 71.5-100%) at a specificity of 83.6% (95% CI 82.3-84.9%) in the GP setting with 17% of children testing positive. In the paediatric outpatient and ED setting, sensitivities were below 92.0%, with specificities below 44.8%.

Conclusions: This clinical prediction rule for identifying children at risk of hospital admission for a serious infection has shown to be extremely sensitive in general practice in an independent validation cohort, making it suitable for ruling out.

BACKGROUND

Acute infection is the most common reason for encounter of children attending ambulatory care.
In a primary care setting, less than 1% of children assessed will ultimately be diagnosed with a serious infection.[1] The incidence of serious infections in children is assumed to be five to ten times higher at the paediatric emergency department (ED).[2] Febrile illness accounts for 20% of all paediatric ED visits.[3]
Serious infections in children are usually defined as sepsis (including bacteraemia), meningitis, pneumonia, complicated urinary tract infection, bacterial gastroenteritis with dehydration, osteomyelitis, and cellulitis.[4] The mortality of meningococcal disease can be as high as 14%.[5] In addition, approximately 7% of children who survive bacterial meningitis suffer from hearing loss.[6]
Serious infections are rare in children in developed countries, but associated with considerable morbidity and mortality.[7] In Flanders, infectious diseases are responsible for 13.8% of all deaths in children under the age of one year, and for 4.6% of deaths in children aged 1 to 14 years.[8] These numbers are comparable to death rates previously reported in the UK.[9]
Serious infections need to be distinguished from the vast majority of self-limiting infections in children. Those few children with a serious infection can present at an early stage when the severity of the infection is not yet apparent.[7] At that point, their symptoms tend to mimic those of children with a non-serious infection. The rapid deterioration could cause a diagnosis to be missed at first contact, sometimes with severe consequences. Early recognition and adequate referral of serious infections are of vital importance to avoid complications. A faster and more accurate recognition of serious diseases could prevent unnecessary investigations, referrals, treatments and hospitalizations in children without serious infection, avoiding traumatic experiences for the child, parental concerns and health care expenditures.

Assessment of serious infections

Clinicians use signs and symptoms to assess the probability of a serious infection and to decide on further management. Clinical prediction rules and guidelines may assist in the early recognition of serious infections. To investigate the predictive value of these signs and symptoms, Van den Bruel et al. conducted a study, which prospectively included over 4000 children, resulting in a 4-step decision tree.[10] This decision tree is easy to interpret, facilitating its use in clinical practice. Although it demonstrated high sensitivity after retrospective validation in another primary care dataset using approximations for gut feeling and dyspnoea, (**Chapter 1**) prospective validation had not been performed as yet.

As described in **Table 1.1a** this decision tree consists of 4 clinical features: the clinician's gut feeling "something is wrong", "dyspnoea", "temperature above 39.95°C" and "diarrhoea in children between 1 and 2.5 years of age".
If yes to any of these 4 sequential questions, the tree is considered positive, reaching a sensitivity and negative predictive value of nearly 100% in the derivation study. The probability of having a serious infection in children testing positive and thus indicating referral for further testing, however, was approximately 6%. Nevertheless, this algorithm demonstrated the highest sensitivity after validation in another primary care dataset, as described in **Chapter 1**.

In this study, we aim to validate this decision tree in a new population diagnosing serious infection in acutely ill children in ambulatory care.
The results of adding results of a point-of-care C-reactive protein test will be reported in **Chapter 5**.

METHODS

Design
This is a prospective diagnostic accuracy study in ambulatory care (defined as general practice, paediatric outpatient clinics or ED).

Participants
Children aged 1 month to 16 years, presenting to a general practitioner (GP) or paediatrician in Flanders, Belgium, with an acute illness were included consecutively from February 15th 2013 to February 28th 2014. Physicians were instructed to recruit children consecutively during the inclusion period. If a physician included less than five children over the study period, the assumption of consecutive inclusion was probably violated, and his or her results were subsequently excluded from the analysis.

Illness episode
Children were included with an acute illness for a maximum of 5 days. Children were excluded if the acute illness was caused by purely traumatic or neurological conditions, intoxication, psychiatric or behavioural problem, or an exacerbation of a known chronic condition.
If a physician included the same child twice within 5 days, we considered the second registration a consequence of the same illness episode and discarded it from the analysis.

Index tests
We asked physicians to perform a thorough clinical assessment of every child, registering items based on experience from previous research and clinical consensus of an international team of clinicians and researchers,[11] such as measurement of the NICE traffic light system, the Yale Observation Scale, the 4-step decision tree, and vital signs, such as a pulse oximetry.[11-13]
In total, 76 clinical features were scored with 28 features from history taking, 38 from clinical examination and point-of-care testing (see **Chapter 5**) and 10 features from diagnosis and management.

The clinician recorded the clinical features, preliminary diagnosis and planned actions (e.g. investigations, treatment or referral) on a case report form (CRF)**.** We provided every physician with a codebook, explaining every feature to be scored on the CRF. A full list of all features can be found in **Appendix 3.1**.

4-step Decision Tree
We asked physicians to score the 4-step decision tree, as developed by Van den Bruel et al.[10].
"Something is wrong" was defined as a subjective gut feeling of the physician that something is out of the ordinary. "Dyspnoea" was defined as difficult or laboured breathing. "Body temperature" was defined as the highest body temperature measured by parents or the physician during the illness episode. Before analysis 0.5°C was added to temperatures measured under the axilla, or with a tympanic thermometer.[14, 15]
"Diarrhoea" was defined as loose or watery stools, increased in frequency and volume.[16]
In addition to the clinical features included in the 4-step decision tree, parents were asked if their child's illness was different from previous illnesses, and clinicians whether the child appeared seriously ill because both features have been shown to be of diagnostic value, similar to gut feeling something is wrong, in the derivation study.[10]
All features were scored as "yes" when present, "no" when absent, and "?" when they could not be evaluated.

Vital signs
The vital signs: temperature (and the site of temperature taking), respiratory rate, heart rate, oxygen saturation and capillary refill time were measured, each according to their respective standardized method.[17]
All general practitioners (GP) were asked to measure pulse oximetry by means of a paediatric finger pulse oximeter (CMS50QA, Contec™ Medical Systems, China), which was provided specifically for this study, measuring oxygen saturation and pulse rate.

A small-scale pilot study was performed to determine the appropriate age requirements for the device and agreement with a large-size pulse oximeter, showing that agreement was sufficient, except in children under the age of three. Accordingly, clinicians were advised not to use the device in this age group. Paediatricians were given the choice to either use the provided finger pulse oximeter, or rather use their own large-size pulse oximeter, appropriate for all age ranges.

Target condition
The target condition was hospital admission (for more than 24 hours) for a serious infection, which was any of the following:

- sepsis (including bacteraemia) with pathogenic bacteria isolated from haemoculture as the reference standard
- meningitis (viral or bacterial) with a positive lumbar puncture (pleocytosis in cerebrospinal fluid and identification of bacteria or a virus) as the reference standard
- appendicitis with a histological diagnosis as the reference standard
- pneumonia (viral or bacterial) with an infiltrate seen on chest X-ray as the reference standard
- osteomyelitis (pathogens from bone aspirate as the reference standard, or if unavailable with a MRI or bone scan suggestive for osteomyelitis)
- cellulitis (acute suppurative inflammation of the subcutaneous tissues)
- bacterial gastro-enteritis with dehydration (pathogen isolated from stool culture)
- complicated urinary tract infection (positive urine culture (>10^5/ml pathogens of a single species) and systemic effects such as fever)

To avoid missing admissions in children with serious infection, the outcome was verified by three complementary methods:
(I) a thorough search of the electronic medical records of all hospitals within the referral region of the participating physicians,
(II) an interview with each participating GP
(III) a diary completed by parents for children recruited in general practice, recording the date of recovery.

If methods (II) and (III) showed evidence of a hospital admission initially not captured by method (I), attempts were made to obtain information of this additional hospital. Children were considered as not having a serious infection if hospital records showed no evidence for a serious infection. In cases when no definitive adjudication could be made based on the above criteria, a steering committee consisting of clinicians involved in teaching and training in acute paediatric care took the final decision, using all available information.

Sample size
Sample size calculations were based on the assumption that prevalence and diagnostic value of the decision tree would be similar to those reported by Van den Bruel and colleagues.
Assuming a prevalence of 0.9%, recruiting 6500 children would result in 59 cases. This would provide us with a margin of error of 12% around our estimate of sensitivity. For an expected sensitivity of 97%, our 95% confidence interval (95% CI) would range from 85-100%.

We aimed to include 6500 acute episodes in children (in 88 general practices and 12 paediatric units) over a period of 12 months.

Informed consent
Parents were informed through posters in the waiting room, as well as flyers, with a short comprehensive description of the background, aims and requirements to participate. Physicians informed every eligible child and their parent(s), delivering an information leaflet and requesting formal approval. Parents were asked to sign a written informed consent form, including permission to access the hospital medical record in case of a possible admission. We provided adjusted information leaflets and consent forms for minors below and above 12 years of age. Baseline characteristics of children (or their parents) declining to participate were recorded on a separate form by the GP to assess potential selection bias.

Ethics
The protocol of this study was approved by the Ethical Review Board of the University Hospitals/KU Leuven, under reference ML8601 as well as all participating institutions. All children's parents were requested to provide written informed consent. As soon as all hospitals within the referral region of all participating GPs were known, these centres were submitted for formal ethical approval by the coordinating and local ethical review boards.

Statistical Analysis

I. Exploratory analysis
First, the accuracy of each clinical feature to diagnose serious infections was analysed and reported in sensitivity, specificity, positive and negative likelihood ratios, and positive and negative predictive values with their 95% confidence intervals (CI) for both the GP and specialist setting (paediatric outpatient and ED setting combined). A correction of 0.5 was added to every cell in case of an empty cell in a 2 x 2 table.

To evaluate the discriminative value of the continuous measures, we constructed Receiver-Operating-Characteristic (ROC) curves to assess their value in both the GP and specialist setting.
In addition, continuous variables, such as vital signs, were dichotomized based on previous research and the NICE guideline "Feverish illness in children".[7, 17] The scoring of capillary refill time in seconds was analysed as a categorical variable, since most physicians scored this above or below 2 seconds.

II. Primary analysis: validation of the 4-step decision tree
The diagnostic accuracy of the 4-step decision tree was validated in the entire group and in three pre-defined subgroups according to setting: general practice, outpatient paediatric care and the ED. In addition, we performed subgroup analyses for pneumonia, complicated urinary tract infections and a composite outcome of sepsis and meningitis.
Instead of limiting our analyses to complete cases, reducing the total number of children available for analysis, the validation of the 4-step decision tree was performed in all children, applying the exact same missing value categorizations for every decision tree variable as provided by the classification and regression tree (CART) analysis in the derivation study.

III. Secondary analysis
Optimizing thresholds for current data
We optimized the classification of the tree by recalibrating the thresholds of the features in the decision tree using CART analysis, keeping the structure of the tree constant.

Pragmatic thresholds for current data
To improve clinician compliance, a pragmatic approach was used to create a more comprehensive decision tree with easy-to-remember thresholds for temperature and age, relevant in clinical practice:
- temperature of 40°C or 39.5°C (instead of 39.95°C or 39.2°C)
- age below 3 years of age (instead of 3.3)

Sensitivity analyses were performed, comparing the results of all illness episodes versus illness episodes based on the first inclusion of children during the study period to avoid clustering based on recurring admissions in the same children.

All analyses were performed with Excel (Microsoft Corporation, Redmond, USA), Stata software (version 11.2; Stata Corp., College Station, TX, USA), and JMP Statistical Discovery (version Pro 11.1.1; SAS Institute Inc., Cary, NC, USA).

RESULTS

Baseline characteristics

Children were recruited across Flanders at 92 GP surgeries, 6 outpatient paediatric clinics and 6 emergency departments. (**Appendix 3.2**) In total, 276 physicians participated in this study of which 170 were GPs and 106 were paediatricians: 33% were male, with a median of 13 years of clinical practice experience (range 0 – 40 years).

We obtained 8962 inclusions between February 15th 2013 and February 28th 2014. **Appendix 3.3** illustrates children were included in the study at a constant rate throughout the year.

Figure 3.1 shows the inclusion flow, resulting in 8664 inclusions available for analysis on 7355 unique children, with 88% of these children (n=6472) included only once during the study period.

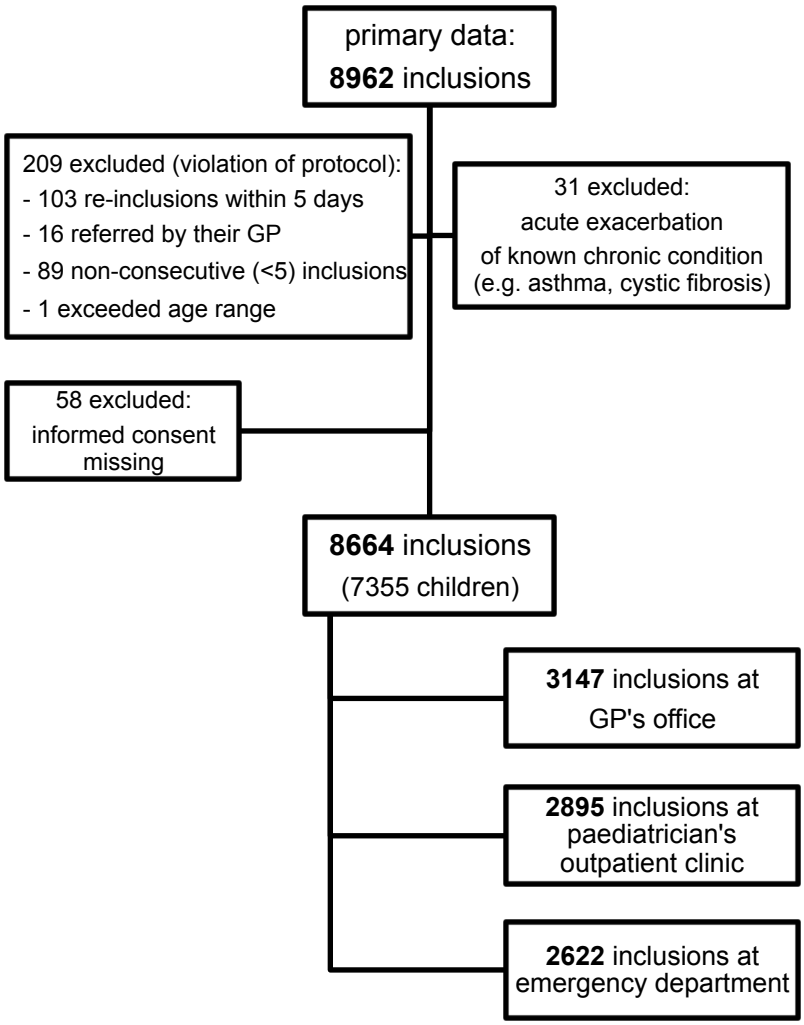

Figure 3.1: Flowchart of recruited children

Children had a median age of 2.1 years (IQR 1-4.4) and 3897 were boys (53.0%). (**Table 3.1**) Children for whom informed consent for recruitment was not obtained (n=77) had a median age of 4 years (interquartile range 5.6) with 56.6% boys.

Table 3.1: Baseline characteristics for inclusions in children with or without a serious infection

Baseline characteristics	inclusions in children with serious infection (n=283)	inclusions in children without serious infection (n=8381)
median age in years (IQR)	1.8 (0.8-4.2)	2 (1-4.1)
sex, male (%)	150 (53.0)	4460 (53.3)
recruited at GP's office (n=3147)	11	3136
recruited at paediatric outpatient clinic (n=2895)	75	2820
recruited at emergency department (n=2622)	197	2425
final outcome (admission >24h with)		
sepsis	10	0
meningitis	17	0
appendicitis	15	0
pneumonia	163	0
osteomyelitis	0	0
cellulitis	3	0
bacterial gastro-enteritis with dehydration	21	0
complicated urinary tract infection	54	0
non-serious infection	0	8381

IQR: interquartile range; GP: general practitioner; h: hours

Clinical features

Appendix 1 lists the clinical features and the number of missing data for every variable with a median of 3.9% (range 0.0 to 32.0%) with the highest numbers for the vital signs measurements.

Outcome verification

- hospital records of all recruited children were checked in all hospitals (60 in total), for participating GPs within their referral region and for paediatricians at the recruiting hospital (13144 records in total).
- interviewing GPs yielded follow up data of 94% of children recruited in the GP setting.
- 1450 (46%) diaries were collected for children recruited at the GP's office.

1025 children were admitted to hospital for more than 24 hours, of which 283 had a serious infection according to our outcome definition.

The remaining 742 children were admitted for either a non-serious viral infection (mostly dehydration as a result of pharyngitis, gastro-enteritis or hypoxia as a result of bronchiolitis) or an observation >24 hours in children suspected of a serious infection, but eventually diagnosed with a non-serious condition. No patient died during the study period.

The prevalence of serious infections was 3.3% (95% CI 2.9 - 3.6%) for all inclusions in children, increasing from 0.3% in the GP setting over 2.6% in the paediatric outpatient setting to 7.5% in the ED setting (confidence intervals not overlapping).

We found only 11 cases of serious infection in the GP setting, of which eight had pneumonia, two a complicated urinary tract infection and one appendicitis. No sepsis or meningitis cases were identified in the GP setting, whereas 27 cases of sepsis and meningitis were identified in the specialist settings. 16 children with meningitis had a viral (mostly Enterovirus or Herpes simplex) and one had a bacterial (Group B Streptococcus) meningeal infection. Five out of the 10 children diagnosed with sepsis, had a positive blood culture for Streptococcus pneumoniae, one had Haemophilus influenzae type B (despite evidence of prior immunization), one Neisseria meningitidis, and three had uropathogenic bacteria (such as Escherichia coli).

The age distribution of children with a serious infection and the total population is depicted in **Figure 3.2**.

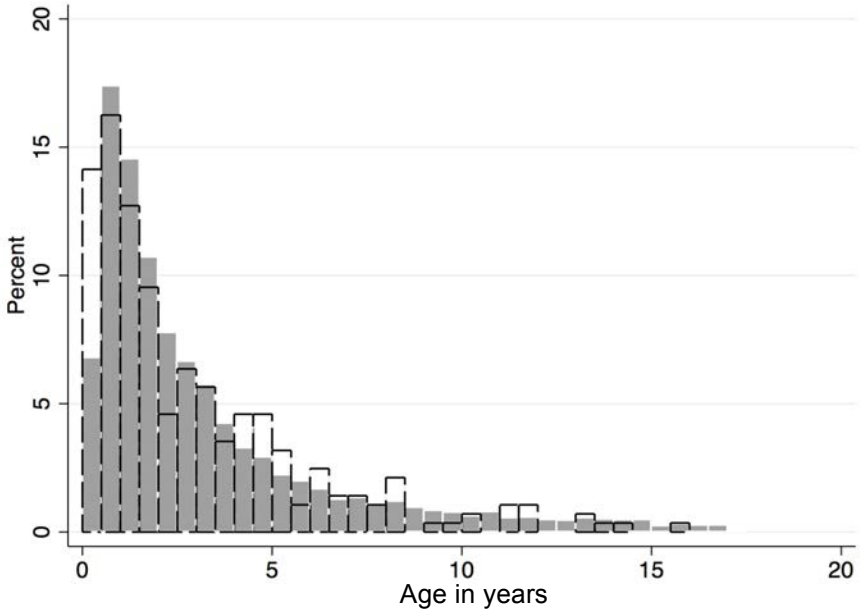

Figure 3.2: Percentage age distribution of serious infections in comparison with total population (per cent)
Dashed transparent black plot represents the percentage age distribution of all serious infections; grey plot represents the age distribution of the total population.

I. Exploratory analysis
Overall the diagnostic accuracy of the presenting signs and symptoms in both the GP setting and specialist setting (paediatric outpatient clinic and ED combined) are listed in **Appendix 3.4**.

In the GP setting, sensitivities were low: only gut feeling, fever of more than 1 day, eating or drinking less, and appearing less active, had sensitivities above 80%. Parental statement that the illness was different from previous illnesses identified 2 of the 11 cases of serious infection in the GP setting and only 5 of these 11 cases appeared seriously ill to their GP, although both features had specificities above 86%. The alarm signs: reduced consciousness, bloody diarrhoea, inconsistent speech, abnormal skin turgor and fontanel tension, petechial rash, meningeal irritation, nasal flaring, cyanosis, reduced peripheral circulation and peritoneal irritation all had specificities above 99%.

In ambulatory paediatrics and the ED, overall sensitivities were even lower, with only fever duration >1 day and fever not reducing to normal temperatures with antipyretics having sensitivities above 80%.

The ROC curves for the vital signs (temperature, breathing rate, heart rate and oxygen saturation) per setting are shown in **Appendix 3.5.**

Overall the area under the curves for the vital signs measurements were low (0.58-0.69), except for breathing rate in the GP setting which had an AUC of 0.80, probably due to the high number of pneumonia cases in this setting.
Due to the limitations of the provided pulse oximeter, only a limited number of oxygen saturation readings were available in the GP setting precluding any reliable analysis.

II. Primary analysis: original validation for any serious infection
Table 3.2 shows the validation results of the 4-step decision tree in all settings together and each setting separately.

General practice
The decision tree reached a sensitivity of 100% (95% CI 71.5-100%), with a specificity of 77.7% (95% CI 76.2-79.1%) in the GP setting.

Paediatric outpatient clinic
In the paediatric outpatient setting the validation of the 4-step decision tree resulted in a sensitivity of 82.7% (95% CI 72.2-90.4%) at a specificity of 60.5% (95% CI 58.7-62.3%).

Emergency department

Validating the 4-step decision tree in the population seen at the emergency department resulted in a sensitivity of 69.5% (95% CI 62.6-75.9%) and a specificity of 56.0% (95% CI 54.0-58.0%).

Table 3.2: Results of validation analysis of the 4-step decision tree for all serious infections

setting	prevalence (%) (n inclusions)		all serious infections		
			validation	optimal cut-offs	pragmatic cut-offs
all	3.3 (8664 inclusions)	sens	**74.2** (68.7 - 79.2)	**89.8** (85.6 - 93.0)	**83.7** (78.9 - 87.8)
		spec	**65.6** (64.6 - 66.6)	**47.2** (46.1 - 48.2)	**52.6** (51.6 - 53.7)
		LR+	**2.2** (2.0 - 2.3)	**1.7** (1.6 - 1.8)	**1.8** (1.7 - 1.9)
		LR-	**0.4** (0.3 - 0.5)	**0.2** (0.2 - 0.3)	**0.3** (0.2 - 0.4)
		PPV	**6.8** (5.9 - 7.7)	**5.4** (4.8 - 6.1)	**5.6** (5.0 - 6.4)
		NPV	**98.7** (98.4 - 99.0)	**99.3** (99.0 - 99.5)	**99.0** (98.6 - 99.2)
		%pos	**35.7**	**54.0**	**48.5**
GP	0.3 (3147 inclusions)	sens	**100** (71.5 - 100)	**100** (71.5 - 100)	**100** (71.5 - 100)
		spec	**77.7** (76.2 - 79.1)	**85.4** (84.1 - 86.6)	**83.6** (82.3 - 84.9)
		LR+	**4.3** (3.8 - 4.9)	**6.6** (5.7 - 7.6)	**5.9** (5.1 - 6.8)
		LR-	**0.1** (0.0 - 0.8)	**0.0** (0.0 - 0.7)	**0.0** (0.0 - 0.8)
		PPV	**1.6** (0.8 - 2.8)	**2.4** (1.2 - 4.2)	**2.1** (1.1 - 3.7)
		NPV	**100** (99.8 - 100)	**100** (99.9 - 100)	**100** (99.9 - 100)
		%pos	**23**	**15**	**17**
Paed	2.6 (2895 inclusions)	sens	**82.7** (72.2 - 90.4)	**92.0** (83.4 - 97.0)	**92.0** (83.4 - 97.0)
		spec	**60.5** (58.7 - 62.3)	**44.8** (43.0 - 46.7)	**44.8** (43.0 - 46.7)
		LR+	**2.1** (1.9 - 2.3)	**1.7** (1.6 - 1.8)	**1.7** (1.6 - 1.8)
		LR-	**0.3** (0.2 - 0.5)	**0.2** (0.1 - 0.4)	**0.2** (0.1 - 0.4)
		PPV	**5.3** (4.0 - 13.2)	**4.3** (3.3 - 5.3)	**4.3** (3.3 - 5.3)
		NPV	**99.2** (98.7 - 99.6)	**99.5** (99.0 - 99.8)	**99.5** (99.0 - 99.8)
		%pos	**40.6**	**56.1**	**56.1**
ED	7.5 (2622 inclusions)	sens	**69.5** (62.6 - 75.9)	**87.8** (82.4 - 92.0)	**80.2** (73.9 - 85.5)
		spec	**56.0** (54.0 - 58.0)	**33.1** (31.2 - 35.0)	**37.0** (35.1 - 38.9)
		LR+	**1.6** (1.4 - 1.8)	**1.3** (1.2 - 1.4)	**1.3** (1.2 - 1.4)
		LR-	**0.5** (0.4 - 0.7)	**0.4** (0.3 - 0.5)	**0.5** (0.4 - 0.7)
		PPV	**11.4** (9.7 - 13.3)	**9.6** (8.3 - 11.1)	**9.4** (8.0 - 10.9)
		NPV	**95.8** (94.6 - 96.8)	**97.1** (95.7 - 98.1)	**95.8** (94.3 - 97.0)
		%pos	**45.9**	**68.5**	**64.3**

GP: general practice; Paed: paediatric outpatient clinic; ED: emergency department; prevalence: prevalence of serious infection; n inclusions: number of inclusions in each setting; sens: sensitivity; spec: specificity; LR+: positive likelihood ratio; LR-: negative likelihood ratio; PPV: positive predictive value; NPV: negative predictive value; %pos: percentage of children testing positive; all diagnostic characteristics are given with their respective 95% confidence intervals in brackets.

Table 3.3: Results of validation analysis of the 4-step decision tree in the different outcome categories

setting		subgroups of serious infection		
		pneumonia	UTI	sepsis/meningitis
all	sens	**80.4** (73.4 - 86.2)	**66.7** (52.5 - 78.9)	**74.1** (53.7 - 88.9)
	spec	**64.8** (63.8 - 65.8)	**64.1** (63.1 - 65.2)	**54.2** (53.1 - 55.2)
	LR+	**2.3** (2.1 - 2.5)	**1.9** (1.5 - 2.3)	**1.6** (1.3 - 2.0)
	LR-	**0.3** (0.2 - 0.4)	**0.5** (0.4 - 0.5)	**0.5** (0.3 - 0.9)
	PPV	**4.2** (3.5 - 5.0)	**1.2** (0.8 - 1.6)	**0.5** (0.3 - 0.8)
	NPV	**99.4** (99.2 - 99.6)	**99.7** (99.5 - 99.8)	**99.9** (99.7 - 99.9)
GP	sens	**100** (63.1 - 100)	**100** (15.8 - 100)	no cases
	spec	**79.2** (77.7 - 80.6)	**88.5** (87.3 - 89.5)	
	LR+	**4.5** (3.8 - 5.4)	**7.2** (4.3 - 12.1)	
	LR-	**0.1** (0.0 - 1.0)	**0.2** (0.0 - 2.4)	
	PPV	**1.2** (0.5 - 2.3)	**0.5** (0.1 - 2.0)	
	NPV	**100** (99.9 - 100)	**100** (99.9 - 100)	
Paed	sens	**84.3** (71.4 - 93.0)	**73.3** (44.9 - 92.2)	**100** (39.8 - 100)
	spec	**59.9** (58.1 - 61.7)	**59.3** (57.5 - 61.1)	**63.2** (61.4 - 64.9)
	LR+	**2.1** (1.9 - 2.4)	**1.8** (1.3 - 2.5)	**2.4** (1.8 - 3.3)
	LR-	**0.3** (0.1 - 0.5)	**0.5** (0.2 - 1.0)	**0.2** (0.0 - 2.2)
	PPV	**3.6** (2.6 - 4.9)	**0.9** (0.5 - 1.7)	**0.4** (0.1 - 1.0)
	NPV	**99.5** (99.1 - 99.8)	**99.8** (99.4 - 99.9)	**100** (99.8 - 100)
ED	sens	**76.9** (67.6 - 84.6)	**62.2** (44.8 - 77.5)	**69.6** (47.1 - 86.8)
	spec	**54.9** (53.0 - 56.9)	**53.9** (51.9 - 55.8)	**41.9** (40.0 - 43.9)
	LR+	**1.7** (1.5 - 1.9)	**1.4** (1.0 - 1.7)	**1.2** (0.9 - 1.6)
	LR-	**0.4** (0.3 - 0.6)	**0.7** (0.5 - 1.1)	**0.7** (0.4 - 1.4)
	PPV	**6.6** (5.3 - 8.1)	**1.9** (1.2 - 2.8)	**1.1** (0.6 - 1.7)
	NPV	**98.3** (97.5 - 98.9)	**99.0** (98.3 - 99.5)	**99.4** (98.7 - 99.7)

GP: general practice; Paed: paediatric outpatient clinic; ED: emergency department; sens: sensitivity; spec: specificity; LR+: positive likelihood ratio; LR-: negative likelihood ratio; PPV: positive predictive value; NPV: negative predictive value; all diagnostic characteristics are given with their respective 95% confidence intervals in brackets; UTI: complicated urinary tract infections; sepsis/meningitis: composite group of sepsis and meningitis cases

Subgroup-analyses for the three main diagnostic categories: pneumonia, complicated urinary tract infection and sepsis or meningitis, are shown in **Table 3.3**.

For pneumonia, the diagnostic characteristics were almost identical to those for the composite outcome of serious infections, which is unsurprising since pneumonia cases make up 58% of all serious infections.

The 4-step decision tree had an even higher specificity for complicated urinary tract infection (88.5% (95% CI 87.3-89.5%)) as compared to validation of the decision tree in the composite outcome of serious infection.

In the paediatric outpatient clinic setting, the tree had a sensitivity of 100% (95% CI 39.8-100%) at a specificity of 63.2% (95% CI 31.4-64.9%) for sepsis and meningitis, although the limited numbers of cases (3 cases of sepsis and 1 case of meningitis) led to a wide confidence interval. The same high sensitivity was not seen in the ED setting, where 23 cases of sepsis or meningitis were found, namely 69.6% (95% CI 47.1-86.8%) at a specificity of 41.9% (95% CI 40.0-43.9%).

II. Secondary analysis

Optimizing thresholds for current data

General practice

If CART analysis was used to define the optimized thresholds for the variables included in the original decision tree, the threshold for "temperature" changed from 39.95°C to 40.7°C, and no threshold for diarrhoea (no serious infections left for this split) which increased the specificity from 77.7 to 85.4% (95% CI 84.1-86.6%). Other variables were left unchanged.

Paediatric outpatient clinic

In this setting changing the thresholds for three variables resulted in the optimal classification:

- gut feeling now classified children as positive only when gut feeling is positive instead of "positive" and "not applicable"
- temperature above 39.5°C (instead of 39.95°C)
- diarrhoea in children <18 months (instead of 14-29 months)

This resulted in a sensitivity of 92.0% (95% CI 83.4-97.0%), however at a lower specificity of 44.8% (95% CI 43.0-46.7%).

Emergency department

Similar to the decision tree at the paediatric outpatient clinic, three variables were changed:

- gut feeling now classified children as positive only when gut feeling is positive instead of "positive" and "not applicable"
- temperature above 39.2°C (instead of 39.95°C)
- diarrhoea in children <39 months (instead of 14-29 months)

A sensitivity of 87.8% (95% CI 82.4-92.0%) was found, however at a specificity of 33.1% (95% CI 31.2-35.0%).

Pragmatic thresholds for current data

General practice

When the pragmatic threshold for temperature was used, sensitivity remained at 100% (95% CI 71.5-100%) but specificity was 83.6% (95% CI 82.3-84.9%) which is higher than the value obtained with the original tree but slightly lower than that obtained with the optimized thresholds for the current data.

Paediatric outpatient clinic

We did not perform any additional analysis here, as the optimized thresholds for the current data chosen by CART in the optimization process can be considered clinically sensible, and easy to apply.

Emergency department

Applying the pragmatic thresholds for temperature and age resulted in a sensitivity of 80.2% (95% CI 73.9-85.5%), still higher than the original tree, but a lower specificity of 37.0% (95% CI 35.1-38.9%).

The sensitivity analyses revealed similar sensitivities and specificities with overlapping confidence intervals for all settings and chosen thresholds in the 7355 (84.9% of all episodes) acute illness episodes, excluding the recurring admissions in the same children.

DISCUSSION

Main findings

Validating the 4-step decision tree in a new but similar population nine years after the derivation study, demonstrated a perfect sensitivity and at a specificity of 84% in the GP setting, thus confirming its usefulness to rule out serious infections in general practice, what it was designed for. This perfect sensitivity compares favourably with current practice in which four of the 11 children that were ultimately admitted to hospital with a serious infection were initially not identified at first presentation.

A clinical decision tree that is able to rule out serious infections is especially useful in low prevalence situations. We found only 11 cases of serious infections in the GP setting (0.3%), most of which were pneumonia (8 cases) and no sepsis or meningitis cases. In the derivation study by Van den Bruel et al. prevalence in the GP setting was a comparable 0.4%.[10]

Validation in the paediatric outpatient clinic and ED settings did not provide useful rule out value, with sensitivities below 83%, however considerably rose to 92% if optimization of the threshold was applied in the paediatric outpatient clinic setting, which had an intermediate prevalence of 2.6% between the GP and ED setting.

A pragmatic approach to the selected thresholds allowed us to enhance overall clarity and ease-of-use of this 4-step decision tree, even resulting in identical diagnostic characteristics in the GP and paediatric outpatient setting.

Strengths and limitations

This is a prospective multi-centre validation study of the 4-step decision tree in a large and similar population of children. Children were recruited consecutively in three different settings covering the whole spectrum of acutely ill children seen at first contact, enhancing the generalizability of these findings.

We obtained almost 9000 inclusions, which makes this study one of the largest cohorts of children with acute illness.[18, 19]

The only other validation study in seven datasets of the 4-step decision tree found similar sensitivities in the single low prevalence dataset, available for validation.[11] Very few studies have validated clinical prediction rules of vital signs and symptoms in acutely ill children in primary care.[7] Most research has been performed in secondary care, with varying results.[12, 18, 20, 21]

To ensure identification of all cases of serious infections, the outcome was measured through three different strategies. However verification of the outcome relied on the quality of hospital records and information obtained during follow-up. Although it is possible that not every child with a serious infection was identified, it is reasonable to assume that our strategies are robust and this was probably avoided.

Measuring the presenting signs and symptoms as mentioned in this study, might have led to additional testing and potentially to a diagnosis of a serious infection (verification bias), further increasing the sensitivity and specificity.[22] Bias due to an inappropriate reference standard could have been present (e.g. normal initial chest X-ray in children with pneumonia), however our standardized follow-up period most likely dealt with this effectively.

Appendicitis was also included in the composite outcome of serious infection. Evidence suggests a wait-and-see policy in certain cases can be beneficial, e.g. cooling down the infection with empirical antibiotic treatment. This shift in management and the relatively unspecific early presentation (stomach ache, fever) supports its inclusion in our composite outcome.[23]

Implications for clinicians

Signs and symptoms are the first available tests to support clinical decision making in primary care.[24] Clinician's feeling that "something is wrong" (gut feeling) is an important predictor of a serious infection.[10] Other red flags, such as cyanosis, rapid breathing, poor peripheral circulation, meningeal irritation and petechial rash also increase the likelihood of a serious infection in ill children, but are rarely present.[7]

We have demonstrated that the 4-step decision tree is both robust and sufficiently sensitive to allow implementation in general practice. 77% of children will safely test negative on the tree. However, it will still identify 23% of acutely ill children (n=711 in our study) as potentially at risk of a serious infection with only 1.5% of these children having a serious infection. Consequently, appropriate additional strategies (point-of-care (POC) testing, safety netting procedures) need to be put in place to avoid unnecessary referrals and use of other medical services.

We still believe that vital signs measurements are of value in evaluating acutely ill children. Physicians often choose not to measure vital signs, assuming them to be normal, however most recent guidelines advice to measure vital signs in acutely ill children,[17, 25] as they might act as a red flag for serious infection.

Future research

Blood tests are only rarely performed in acutely ill children in primary care, due to the need to make management decisions prior to the availability of test results. Very little research has been performed in ambulatory care and none of it in primary care specifically. However, there might be a role for a C-reactive protein POC test to rule out serious infections.[26] POC tests enable physicians to adjust their management according to the immediate test results. They are minimally invasive, with great potential in paediatric care.

Future research might be able to establish the exact role of such tests in the management of acutely ill children presenting to primary care.

ACKNOWLEDGEMENTS

We would like to thank all participating GPs and paediatricians. We would like to thank Frederick Albert, Greet Delvou and Annelien Poppe for daily follow up during the study. We would like to thank IKEA, Belgium, for providing finger puppets. And last but not least, we would like to thank all children and parents who took part in this study.

FUNDING

This study was funded by the National Institute for Health and Disability Insurance (RIZIV, Belgium) under reference CGV n° 2012/235 and the Research Foundation - Flanders (FWO) under reference n° G067509N.

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Appendix 3.1: clinical features and number (%) of missing values

type	variable	values	n/N missing	% missing	n/N "could not be evaluated"	% "could not be evaluated"	n/N "not measured"	% "not measured"
informed consent	setting	1/2/3 (GP/Paed/ED)	0/8664	0.0%	-	-	-	-
	date of birth	date	8/8664	0.1%	-	-	-	-
	sex	0/1 (boy/girl)	3/8664	0.0%	-	-	-	-
age	age in years	# years	3/8664	0.0%	-	-	-	-
history taking	presenting complaints	string variable	99/8664	1.1%	-	-	-	-
	chronic condition	string variable	2770/8664	32.0%	-	-	-	-
	illness is different from previous illnesses	0/1/2 (no/yes/couldnotevaluate)	340/8664	3.9%	106/8664	1.2%	-	-
	child is less active	0/1/2 (no/yes/couldnotevaluate)	228/8664	2.6%	18/8664	0.2%	-	-
	child is sleepy	0/1/2 (no/yes/couldnotevaluate)	260/8664	3.0%	22/8664	0.3%	-	-
	child is hard to wake up	0/1/2 (no/yes/couldnotevaluate)	291/8664	3.3%	16/8664	0.2%	-	-
	child cries a lot	0/1/2 (no/yes/couldnotevaluate)	253/8664	2.9%	14/8664	0.2%	-	-
	child has abnormal behaviour	0/1/2 (no/yes/couldnotevaluate)	275/8664	3.2%	39/8664	0.5%	-	-
	child's speech is inconsistent	0/1/2 (no/yes/couldnotevaluate)	303/8664	3.5%	285/8664	3.3%	-	-
	fever present?	0/1/2 (no/yes/couldnotevaluate)	537/8664	6.2%	165/8664	1.9%	-	-
	highest fever measured	temp in tt.tt °C	483/8664	5.6%	-	-	-	-
	duration of fever	# days	868/8664	10.0%	-	-	-	-
	fever improvement with antipyretics	0/1/2 (no/yes/couldnotevaluate)	995/8664	11.5%	541/8664	6.2%	-	-
	diarrhoea	0/1/2 (no/yes/couldnotevaluate)	201/8664	2.3%	20/8664	0.2%	-	-
	bloody diarrhoea	0/1/2 (no/yes/couldnotevaluate)	393/8664	4.5%	11/8664	0.1%	-	-
	stomach ache	0/1/2 (no/yes/couldnotevaluate)	344/8664	4.0%	400/8664	4.6%	-	-
	vomiting	0/1/2 (no/yes/couldnotevaluate)	257/8664	3.0%	25/8664	0.3%	-	-
	persistent vomiting	0/1/2 (no/yes/couldnotevaluate)	444/8664	5.1%	18/8664	0.2%	-	-
	bile-stained vomiting	0/1/2 (no/yes/couldnotevaluate)	496/8664	5.7%	17/8664	0.2%	-	-
	does your child eat and drink less?	0/1/2 (no/yes/couldnotevaluate)	226/8664	2.6%	15/8664	0.2%	-	-
	does your child pee less?	0/1/2 (no/yes/couldnotevaluate)	286/8664	3.3%	159/8664	1.8%	-	-
	short of breath	0/1/2 (no/yes/couldnotevaluate)	340/8664	3.9%	49/8664	0.6%	-	-
	coughing	0/1/2 (no/yes/couldnotevaluate)	169/8664	2.0%	12/8664	0.1%	-	-
	headache	0/1/2 (no/yes/couldnotevaluate)	279/8664	3.2%	513/8664	5.9%	-	-
	neck pain	0/1/2 (no/yes/couldnotevaluate)	297/8664	3.4%	457/8664	5.3%	-	-
observation	gut feeling something is wrong	0/1/2 (no/yes/couldnotevaluate)	334/8664	3.9%	72/8664	0.8%	-	-
	clinical impression child is seriously ill	0/1/2 (no/yes/couldnotevaluate)	282/8664	3.3%	62/8664	0.7%	-	-
	child is irritable	0/1/2 (no/yes/couldnotevaluate)	270/8664	3.1%	7/8664	0.1%	-	-
	child is drowsy	0/1/2 (no/yes/couldnotevaluate)	272/8664	3.1%	3/8664	0.0%	-	-
	child had reduced consciousness	0/1/2 (no/yes/couldnotevaluate)	265/8664	3.1%	2/8664	0.0%	-	-
	child is inconsolable	0/1/2 (no/yes/couldnotevaluate)	271/8664	3.1%	6/8664	0.1%	-	-
	child is moaning	0/1/2 (no/yes/couldnotevaluate)	265/8664	3.1%	7/8664	0.1%	-	-
	child has nasal flaring	0/1/2 (no/yes/couldnotevaluate)	271/8664	3.1%	9/8664	0.1%	-	-
	chestwall retractions	0/1/2 (no/yes/couldnotevaluate)	276/8664	3.2%	8/8664	0.1%	-	-
	child laughs less	0/1/2 (no/yes/couldnotevaluate)	273/8664	3.2%	33/8664	0.4%	-	-

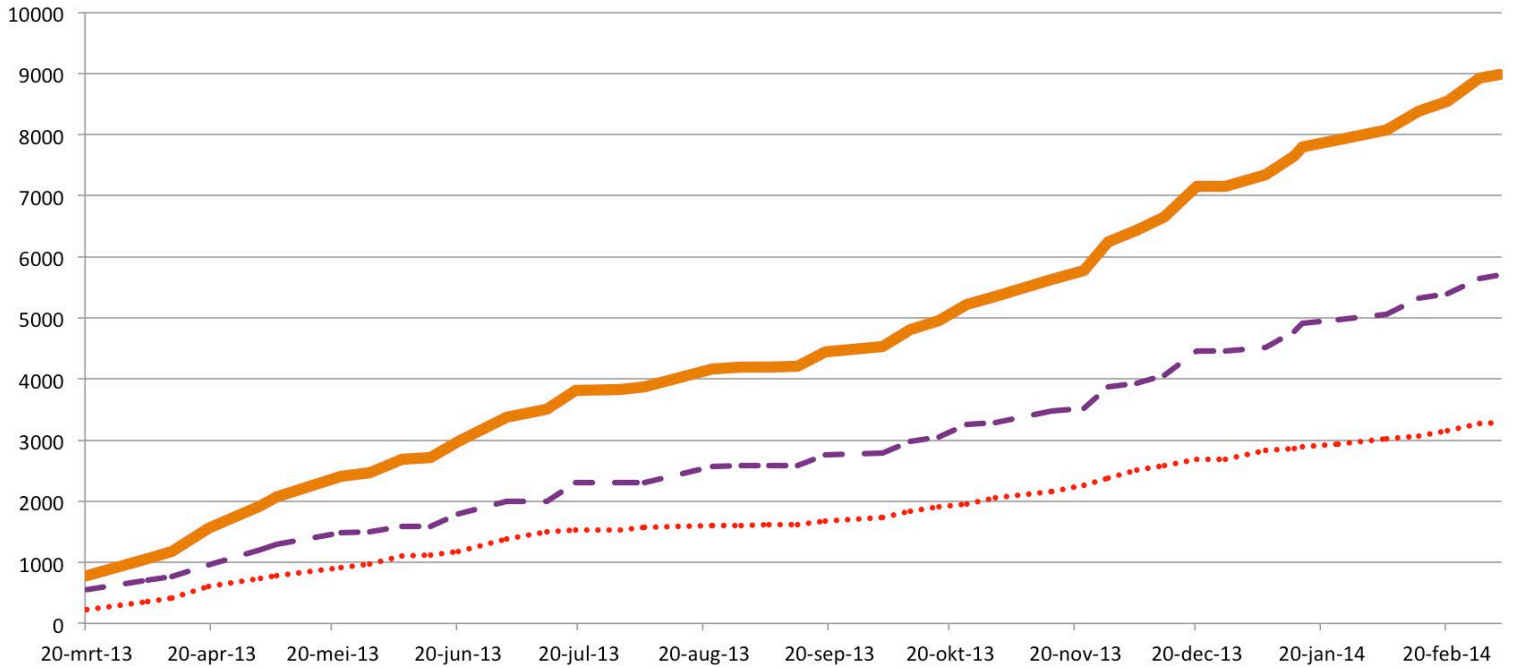
GP: general practice; Paed: paediatric outpatient clinic; ED: emergency department; n/N: number of children with a missing value for this predictor out of all children

Appendix 3.1: clinical features and number (%) of missing values *(continued)*

type	variable	values	n/N missing	% missing	n/N "could not be evaluated"	% "could not be evaluated"	n/N "not measured"	% "not measured"
clinical examination	pus on tonsils	0/1/2 (no/yes/couldnotevaluate)	354/8664	4.1%	16/8664	0.2%	-	-
	signs of acute otitis media	0/1/2 (no/yes/couldnotevaluate)	353/8664	4.1%	43/8664	0.5%	-	-
	bilateral otitis media	0/1/2 (no/yes/couldnotevaluate)	401/8664	4.6%	21/8664	0.2%	-	-
	discharging ears	0/1/2 (no/yes/couldnotevaluate)	496/8664	5.7%	11/8664	0.1%	-	-
	extensive adenopathy	0/1/2 (no/yes/couldnotevaluate)	339/8664	3.9%	11/8664	0.1%	-	-
	redness and or swelling of face	0/1/2 (no/yes/couldnotevaluate)	342/8664	3.9%	4/8664	0.0%	-	-
	purulent conjunctivae	0/1/2 (no/yes/couldnotevaluate)	330/8664	3.8%	3/8664	0.0%	-	-
	bilateral purulent conjunctivae	0/1/2 (no/yes/couldnotevaluate)	353/8664	4.1%	2/8664	0.0%	-	-
	dyspnea	0/1/2 (no/yes/couldnotevaluate)	330/8664	3.8%	13/8664	0.1%	-	-
	crepitations (crackling)	0/1/2 (no/yes/couldnotevaluate)	334/8664	3.9%	11/8664	0.1%	-	-
	reduced breathing sounds	0/1/2 (no/yes/couldnotevaluate)	348/8664	4.0%	9/8664	0.1%	-	-
	rhonchi	0/1/2 (no/yes/couldnotevaluate)	292/8664	3.4%	8/8664	0.1%	-	-
	cyanosis	0/1/2 (no/yes/couldnotevaluate)	345/8664	4.0%	6/8664	0.1%	-	-
	peritoneal irritation	0/1/2 (no/yes/couldnotevaluate)	507/8664	5.9%	20/8664	0.2%	-	-
	petechial rash	0/1/2 (no/yes/couldnotevaluate)	332/8664	3.8%	3/8664	0.0%	-	-
	meningeal irritation	0/1/2 (no/yes/couldnotevaluate)	344/8664	4.0%	10/8664	0.1%	-	-
	reduced peripheral circulation	0/1/2 (no/yes/couldnotevaluate)	341/8664	3.9%	5/8664	0.1%	-	-
	pale	0/1/2 (no/yes/couldnotevaluate)	333/8664	3.8%	6/8664	0.1%	-	-
	skin turgor	0/1/2 (no/yes/couldnotevaluate)	342/8664	3.9%	17/8664	0.2%	-	-
	fontanel tension	0/1/2/3/4 (normal/bulged/ couldnotevaluate/sunken/not applicable)	368/8664	4.2%	27/8664	0.3%	-	-
	swollen limb, non weight bearing extremity	0/1/2 (no/yes/couldnotevaluate)	2354/8664	27.2%	16/8664	0.2%	-	-
	measured temperature	temp in tt.tt °C (couldnotevaluate/notmeasured)	1484/8664	17.1%	31/8664	0.4%	555/8664	6.4%
	highest temperature (measured or reported)	temp in tt.tt °C (couldnotevaluate/notmeasured)	420/8664	4.8%	3/8664	0.0%	113/8664	1.3%
	breathing rate	#/min	2671/8664	30.8%	183/8664	2.1%	3419/8664	39.5%
	heart rate	#/min	2466/8664	28.5%	180/8664	2.1%	2898/8664	33.4%
	oxygen saturation	%	2567/8664	29.6%	212/8664	2.4%	3195/8664	36.9%
	capillary refill	# sec	2373/8664	27.4%	25/8664	0.3%	2595/8664	30.0%
CRP	CRP value fingerstick	mg/L	1848/8664	21.3%	-	-	-	-
diagnosis	working diagnosis	string variable	202/8664	2.3%	-	-	-	-
treatment	antipyretics	0/2/3/4/5 (none/couldnotevaluate/ paracetamol/ibuprofen/both)	781/8664	9.0%	6/8664	0.1%	-	-
	antibiotics	0/1 (no/yes)	1162/8664	13.4%	-	-	-	-
	delayed antibiotic prescription	0/1 (no/yes)	2014/8664	23.2%	-	-	-	-
	I believe the parents expect antibiotics	0/1/2 (no/yes/couldnotevaluate)	2426/8664	28.0%	519/8664	6.0%	-	-
referral/tests	extra tests?	0/1/2 (no/yes/couldnotevaluate)	1120/8664	12.9%	3/8664	0.0%	-	-
	blood test?	0/1 (no/yes)	2554/8664	29.5%	-	-	-	-
	X-ray?	0/1 (no/yes)	2636/8664	30.4%	-	-	-	-
	urine test?	0/1 (no/yes)	1795/8664	20.7%	-	-	-	-
	referral (GP setting) / admission (hospital setting)	0/1/2 (no/yes/couldnotevaluate)	1777/8664	20.5%	22/8664	0.3%	-	-

n/N: number of children with a missing value for this predictor out of all children; sec: seconds; GP: general practice

Appendix 3.2: Recruiting GP surgeries and hospitals across Flanders
Dots represent recruiting general practice surgeries; crosses represent recruiting hospitals.



Appendix 3.3: Total inclusions in children between February 15th 2013 and February 28th 2014
Dotted line represents inclusions in children recruited by general practitioners; dashed line represents inclusions in children recruited by paediatricians.

Appendix 3.4: bivariable analyses of clinical features to identify serious infections in general practice setting

type	variable	sensitivity	95% CI		specificity	95% CI		LR+	95% CI		LR-	95% CI		PPV	95% CI		NPV	95% CI	
history taking	illness is different from previous illnesses	**20.0**	2.5	55.6	**86.1**	84.8	87.3	**1.4**	0.4	5.0	**0.9**	0.7	1.3	**0.5**	0.1	1.7	**99.7**	99.4	99.9
	child is less active	**81.8**	48.2	97.7	**60.4**	58.6	62.1	**2.1**	1.6	2.7	**0.3**	0.1	1.1	**0.7**	0.3	1.4	**99.9**	99.6	100.0
	child is sleepy	**72.7**	39.0	94.0	**72.4**	70.8	74.0	**2.6**	1.8	3.8	**0.4**	0.1	1.0	**0.9**	0.4	1.8	**99.9**	99.6	100.0
	child is hard to wake up	**18.2**	2.3	51.8	**97.1**	96.4	97.6	**6.2**	1.7	22.0	**0.8**	0.6	1.1	**2.2**	0.3	7.6	**99.7**	99.4	99.9
	child cries a lot	**63.6**	30.8	89.1	**69.2**	67.5	70.8	**2.1**	1.3	3.2	**0.5**	0.2	1.2	**0.7**	0.3	1.5	**99.8**	99.5	99.9
	child has abnormal behaviour	**20.0**	2.5	55.6	**91.7**	90.6	92.6	**2.4**	0.7	8.4	**0.9**	0.6	1.2	**0.8**	0.1	2.8	**99.7**	99.4	99.9
	child's speech is inconsistent	**9.1**	0.2	41.3	**99.2**	98.8	99.5	**11.6**	1.7	78.5	**0.9**	0.8	1.1	**4.2**	0.1	21.1	**99.7**	99.4	99.8
	highest fever measured ≥ 39.5°C	**27.3**	6.0	61.0	**73.1**	71.1	74.9	**1.0**	0.4	2.7	**1.0**	0.7	1.4	**0.5**	0.1	1.5	**99.5**	99.0	99.8
	highest fever measured ≥ 40.0°C	**18.2**	2.3	51.8	**90.0**	88.6	91.2	**1.8**	0.5	6.4	**0.9**	0.7	1.2	**0.9**	0.1	3.2	**99.5**	99.1	99.8
	fever duration ≥ 1 day	**100.0**	71.5	100.0	**0.6**	0.3	1.1	**1.0**	0.9	1.1	**6.3**	0.4	99.8	**0.5**	0.3	1.0	**100.0**	75.3	100.0
	fever duration ≥ 4 days	**27.3**	6.0	61.0	**91.1**	89.7	92.3	**3.1**	1.2	8.1	**0.8**	0.6	1.2	**1.6**	0.3	4.7	**99.6**	99.2	99.8
	fever improves with antipyretics	**77.8**	40.0	97.2	**9.4**	8.1	10.8	**0.9**	0.6	1.2	**2.4**	0.7	8.1	**0.4**	0.2	0.9	**98.8**	95.8	99.9
	diarrhoea	**20.0**	2.5	55.6	**85.5**	84.2	86.8	**1.4**	0.4	4.8	**0.9**	0.7	1.3	**0.4**	0.1	1.6	**99.7**	99.4	99.9
	bloody diarrhoea	**0.0**	0.0	33.6	**99.7**	99.4	99.9	**15.9**	1.0	256.0	**1.0**	0.8	1.1	**0.0**	0.0	33.6	**99.7**	99.4	99.9
	stomach ache	**60.0**	26.2	87.8	**78.6**	77.1	80.1	**2.8**	1.7	4.7	**0.5**	0.2	1.1	**1.0**	0.4	2.1	**99.8**	99.6	100.0
	vomiting	**30.0**	6.7	65.2	**83.6**	82.2	84.8	**1.8**	0.7	4.7	**0.8**	0.6	1.3	**0.6**	0.1	1.7	**99.7**	99.4	99.9
	persistent vomiting	**0.0**	0.0	33.6	**97.4**	96.8	97.9	**1.9**	0.1	28.6	**1.0**	0.8	1.1	**0.0**	0.0	4.6	**99.7**	99.4	99.9
	bile-stained vomiting	**0.0**	0.0	33.6	**98.8**	98.4	99.2	**4.2**	0.3	64.4	**1.0**	0.8	1.1	**0.0**	0.0	10.0	**99.7**	99.4	99.9
	child eats and drinks less	**90.0**	55.5	99.7	**57.9**	56.2	59.7	**2.1**	1.7	2.6	**0.2**	0.0	1.1	**0.7**	0.3	1.3	**99.9**	99.7	100.0
	child pees less	**40.0**	12.2	73.8	**91.6**	90.6	92.6	**4.8**	2.2	10.3	**0.7**	0.4	1.1	**1.6**	0.4	4.0	**99.8**	99.5	99.9
	short of breath	**50.0**	18.7	81.3	**88.2**	87.0	89.3	**4.2**	2.3	7.9	**0.6**	0.3	1.1	**1.4**	0.4	3.2	**99.8**	99.6	99.9
	coughing	**72.7**	39.0	94.0	**40.3**	38.5	42.0	**1.2**	0.8	1.8	**0.7**	0.3	1.8	**0.4**	0.2	0.8	**99.8**	99.3	100.0
	headache	**10.0**	0.3	44.5	**86.2**	84.8	87.4	**0.7**	0.1	4.7	**1.0**	0.8	1.3	**0.2**	0.0	1.4	**99.6**	99.3	99.8
	neck pain	**0.0**	0.0	30.8	**97.0**	96.3	97.6	**1.5**	0.1	22.7	**1.0**	0.9	1.1	**0.0**	0.0	4.2	**99.6**	99.3	99.8
observation	gut feeling something is wrong	**80.0**	44.4	97.5	**89.0**	87.8	90.1	**7.3**	5.3	10.1	**0.2**	0.1	0.8	**2.4**	1.0	4.6	**99.9**	99.7	100.0
	clinical impression child is seriously ill	**50.0**	18.7	81.3	**91.0**	89.9	92.0	**5.5**	3.0	10.4	**0.6**	0.3	1.0	**1.8**	0.6	4.1	**99.8**	99.6	99.9
	child is irritable	**40.0**	12.2	73.8	**92.1**	91.1	93.3	**5.1**	2.4	10.9	**0.7**	0.4	1.1	**1.6**	0.4	4.1	**99.8**	99.5	99.9
	child is drowsy	**20.0**	2.5	55.6	**96.6**	95.9	97.2	**5.8**	1.7	20.4	**0.8**	0.6	1.1	**1.9**	0.2	6.6	**99.7**	99.5	99.9
	child had reduced consciousness	**10.0**	0.3	44.5	**99.7**	99.4	99.9	**34.0**	4.7	244.0	**0.9**	0.7	1.1	**10.0**	0.3	44.5	**99.7**	99.4	99.9
	child is inconsolable	**0.0**	0.0	30.8	**97.6**	97.0	98.1	**1.9**	0.1	28.7	**1.0**	0.9	1.1	**0.0**	0.0	4.9	**99.7**	99.4	99.8
	child is moaning	**10.0**	0.3	44.5	**98.4**	97.9	98.8	**6.4**	1.0	41.8	**0.9**	0.7	1.1	**2.0**	0.1	10.9	**99.7**	99.4	99.9
	child has nasal flaring	**10.0**	0.3	44.5	**99.4**	99.1	99.7	**17.0**	2.5	115.0	**0.9**	0.7	1.1	**5.3**	0.1	26.0	**99.7**	99.4	99.9
	chestwall retractions	**20.0**	2.5	55.6	**97.8**	97.2	98.3	**9.1**	2.6	32.2	**0.8**	0.6	1.1	**2.9**	0.4	10.1	**99.7**	99.5	99.9
	child laughs less	**70.0**	34.8	93.9	**89.9**	88.8	91.0	**6.9**	4.6	10.6	**0.3**	0.1	0.9	**2.2**	0.9	4.5	**99.9**	99.7	100.0

LR+: positive likelihood ratio; LR-: negative likelihood ratio; PPV: positive predictive value; NPV: negative predictive value; 95% CI: 95% confidence intervals

Appendix 3.4: bivariable analyses of clinical features to identify serious infections in general practice setting *(continued)*

type	variable	sensitivity	95% CI		specificity	95% CI		LR+	95% CI		LR-	95% CI		PPV	95% CI		NPV	95% CI	
clinical examination	pus on tonsils	**70.0**	34.8	93.3	**89.9**	88.8	91.0	**6.9**	4.6	10.6	**0.3**	0.1	0.9	**2.2**	0.9	4.5	**99.9**	99.7	100.0
	signs of acute otitis media	**30.0**	6.7	65.2	**80.9**	79.4	82.2	**1.7**	0.7	4.0	**0.8**	0.6	1.3	**0.5**	0.1	1.5	**99.7**	99.4	99.9
	bilateral otitis media	**20.0**	2.5	55.6	**92.0**	90.9	92.9	**2.5**	0.7	8.7	**0.9**	0.6	1.2	**0.8**	0.1	2.9	**99.7**	99.4	99.9
	discharging ears	**0.0**	0.0	33.6	**98.2**	97.7	98.7	**2.8**	0.2	42.6	**1.0**	0.8	1.1	**0.0**	0.0	6.9	**99.7**	99.4	99.9
	extensive adenopathy	**22.2**	2.8	60.0	**89.4**	88.2	90.5	**2.1**	0.6	7.2	**0.9**	0.6	1.2	**0.6**	0.1	2.2	**99.7**	99.5	99.9
	redness and or swelling of face	**0.0**	0.0	30.8	**95.8**	95.0	96.5	**1.1**	0.1	16.3	**1.0**	0.9	1.1	**0.0**	0.0	2.9	**99.7**	99.4	99.8
	purulent conjunctivae	**0.0**	0.0	30.8	**95.6**	94.8	96.3	**1.0**	0.1	15.6	**1.0**	0.9	1.1	**0.0**	0.0	2.7	**99.7**	99.4	99.8
	bilateral purulent conjunctivae	**0.0**	0.0	30.8	**97.5**	96.8	98.0	**1.8**	0.1	26.9	**1.0**	0.9	1.1	**0.0**	0.0	4.7	**99.7**	99.4	99.8
	dyspnea	**40.0**	12.2	73.8	**94.7**	93.8	95.5	**7.6**	3.5	16.4	**0.6**	0.4	1.1	**2.4**	0.7	6.1	**99.8**	99.5	99.9
	crepitations (crackling)	**10.0**	0.3	44.5	**95.3**	94.5	96.0	**2.1**	0.3	13.8	**0.9**	0.8	1.2	**0.7**	0.0	3.8	**99.7**	99.4	99.9
	reduced breathing sounds	**0.0**	0.0	30.8	**97.9**	97.3	98.3	**2.1**	0.1	31.9	**1.0**	0.9	1.1	**0.0**	0.0	5.5	**99.7**	99.4	99.8
	rhonchi	**50.0**	18.7	81.3	**83.6**	82.2	84.9	**3.1**	1.6	5.7	**0.6**	0.3	1.1	**1.0**	0.3	2.3	**99.8**	99.5	99.9
	cyanosis	**0.0**	0.0	30.8	**99.9**	99.7	100.0	**30.6**	1.8	535.0	**1.0**	0.8	1.1	**0.0**	0.0	60.2	**99.7**	99.4	99.8
	peritoneal irritation	**11.1**	0.3	48.2	**99.4**	99.1	99.6	**18.8**	2.8	126.0	**0.9**	0.7	1.1	**5.3**	0.1	26.0	**99.7**	99.5	99.9
	petechial rash	**0.0**	0.0	30.8	**99.7**	99.4	99.9	**14.6**	0.9	235.0	**1.0**	0.8	1.1	**0.0**	0.0	33.6	**99.7**	99.4	99.8
	meningeal irritation	**0.0**	0.0	30.8	**99.7**	99.4	99.9	**14.5**	0.9	234.0	**1.0**	0.8	1.1	**0.0**	0.0	33.6	**99.7**	99.4	99.8
	reduced peripheral circulation	**0.0**	0.0	30.8	**99.7**	99.1	99.6	**7.5**	0.5	116.0	**1.0**	0.8	1.1	**0.0**	0.0	18.5	**99.7**	99.4	99.8
	pale	**10.0**	0.3	44.5	**95.0**	94.2	95.8	**2.0**	0.3	13.0	**0.9**	0.8	1.2	**0.7**	0.0	3.6	**99.7**	99.4	99.9
	abnormal skin turgor	**0.0**	0.0	30.8	**99.8**	99.5	99.9	**18.3**	1.1	302.0	**1.0**	0.8	1.1	**0.0**	0.0	41.0	**99.7**	99.4	99.8
	abnormal fontanel tension	**0.0**	0.0	45.9	**99.7**	99.4	99.9	**223.1**	1.5	363.0	**0.9**	0.8	1.1	**0.0**	0.0	36.9	**99.8**	99.5	99.9
	swollen limb or non weight bearing extremity	**0.0**	0.0	45.9	**99.5**	99.2	99.8	**14.8**	1.0	228.0	**0.9**	0.8	1.2	**0.0**	0.0	28.5	**99.7**	99.5	99.9
	measured temperature ≥ 39.5°C	**0.0**	0.0	33.6	**96.1**	95.3	96.9	**1.3**	0.1	19.3	**1.0**	0.9	1.1	**0.0**	0.0	4.2	**99.6**	99.2	99.8
	measured temperature ≥ 40.0°C	**0.0**	0.0	33.6	**98.4**	97.7	98.8	**3.0**	0.2	45.6	**1.0**	0.8	1.1	**0.0**	0.0	9.5	**99.6**	99.2	99.8
	highest temperature (measured or reported) ≥ 39.5°C	**27.3**	6.0	61.0	**77.9**	76.3	79.4	**1.2**	0.5	3.2	**0.9**	0.7	1.3	**0.5**	0.1	1.4	**99.6**	99.3	99.8
	highest temperature (measured or reported) ≥ 40.0°C	**18.2**	2.3	51.8	**91.6**	90.5	92.6	**2.2**	0.6	7.6	**0.9**	0.7	1.2	**0.8**	0.1	3.0	**99.7**	99.3	99.8
	breathing rate ≥ 50/min	**33.3**	4.3	77.7	**93.4**	91.7	94.8	**5.0**	1.6	16.0	**0.7**	0.4	1.3	**2.9**	0.4	10.1	**99.6**	98.9	99.9
	heart rate ≥ 150/min	**12.5**	0.3	52.7	**96.3**	95.3	97.2	**3.4**	0.5	21.6	**0.9**	0.7	1.2	**1.6**	0.0	8.7	**99.6**	99.1	99.8
	oxygen saturation ≤ 95%	**0.0**	0.0	52.2	**88.8**	87.0	90.5	**0.7**	0.1	10.6	**1.0**	0.8	1.3	**0.0**	0.0	2.5	**99.6**	99.0	99.9
	capillary refill ≥ 3 seconds	**0.0**	0.0	70.8	**90.4**	88.5	92.0	**1.3**	0.1	17.4	**1.0**	0.7	1.4	**0.0**	0.0	3.3	**99.7**	99.2	99.9

LR+: positive likelihood ratio; LR-: negative likelihood ratio; PPV: positive predictive value; NPV: negative predictive value; 95% CI: 95% confidence intervals

Appendix 3.4: bivariable analyses of clinical features to identify serious infections in specialist setting

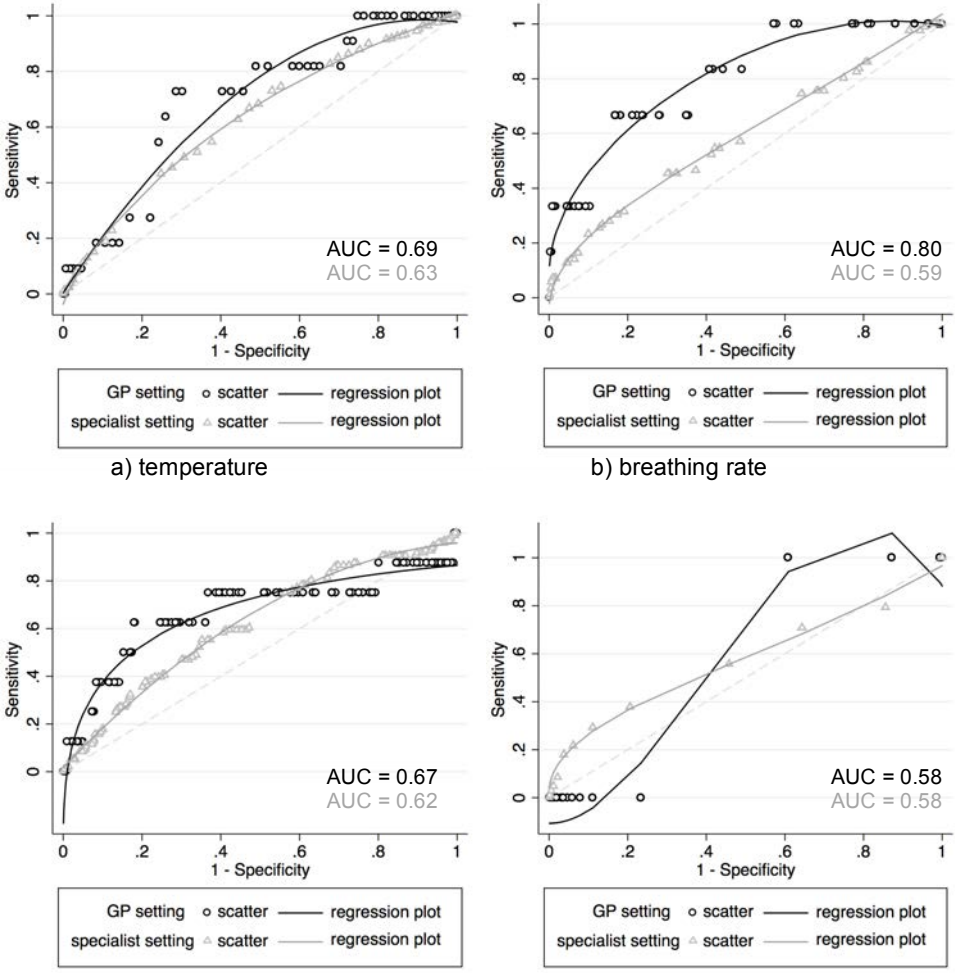
type	variable	sensitivity	95% CI		specificity	95% CI		LR+	95% CI		LR-	95% CI		PPV	95% CI		NPV	95% CI	
history taking	illness is different from previous illnesses	**1.6**	0.4	4.0	**98.9**	98.6	99.2	**1.4**	0.5	3.9	**1.0**	1.0	1.0	**6.8**	1.9	16.5	**95.2**	94.6	95.8
	child is less active	**0.4**	0.0	2.1	**99.7**	99.6	99.9	**1.5**	0.2	11.3	**1.0**	1.0	1.0	**7.1**	0.2	33.9	**95.1**	94.5	95.6
	child is sleepy	**0.4**	0.0	2.1	**99.7**	99.6	99.9	**1.5**	0.2	11.4	**1.0**	1.0	1.0	**7.1**	0.2	33.9	**95.1**	94.5	95.7
	child is hard to wake up	**0.4**	0.0	2.1	**99.8**	99.6	99.9	**2.0**	0.3	15.2	**1.0**	1.0	1.0	**9.1**	0.2	41.3	**95.1**	94.5	95.7
	child cries a lot	**0.0**	0.0	1.4	**99.8**	99.6	99.9	**0.9**	0.1	15.6	**1.0**	1.0	1.0	**0.0**	0.0	30.8	**95.1**	94.4	95.6
	child has abnormal behaviour	**1.9**	0.6	4.5	**99.6**	99.4	99.7	**4.6**	1.8	12.2	**1.0**	1.0	1.0	**19.2**	6.6	39.4	**95.3**	94.6	95.8
	child's speech is inconsistent	**4.7**	2.5	8.1	**97.1**	96.6	97.5	**1.6**	0.9	2.9	**1.0**	1.0	1.0	**7.6**	4.0	12.8	**95.3**	94.6	95.8
	highest fever measured ≥ 39.5°C	**63.7**	57.5	69.6	**52.3**	50.9	53.8	**1.3**	1.2	1.5	**0.7**	0.6	0.8	**7.0**	6.0	8.1	**96.3**	95.4	97.0
	highest fever measured ≥ 40.0°C	**44.1**	38.0	50.5	**73.1**	71.8	74.4	**1.6**	1.4	1.9	**0.8**	0.7	0.9	**8.5**	7.0	10.1	**95.9**	95.2	96.5
	fever duration ≥ 1 day	**98.7**	96.3	99.7	**0.6**	0.4	0.9	**1.0**	1.0	1.0	**2.3**	0.8	6.9	**5.2**	4.6	5.9	**90.0**	73.5	97.9
	fever duration ≥ 4 days	**20.7**	15.7	26.5	**83.0**	81.9	84.2	**1.2**	0.9	1.6	**1.0**	0.9	1.0	**6.3**	4.7	8.3	**95.0**	94.2	95.7
	fever improves with antipyretics	**81.0**	75.2	85.9	**10.3**	9.3	11.3	**0.9**	0.8	1.0	**1.9**	1.4	2.5	**5.0**	4.3	5.8	**90.3**	87.1	92.9
	diarrhoea	**26.8**	21.5	32.6	**79.0**	77.9	80.1	**1.3**	1.0	1.6	**0.9**	0.9	1.0	**6.1**	4.8	7.7	**95.5**	94.8	96.1
	bloody diarrhoea	**2.0**	0.7	4.6	**99.6**	99.4	99.8	**5.5**	2.1	14.7	**1.0**	1.0	1.0	**21.7**	7.5	43.7	**95.3**	94.7	95.8
	stomach ache	**22.5**	17.3	28.3	**86.9**	85.9	87.8	**1.7**	1.3	2.2	**0.9**	0.8	1.0	**7.8**	5.9	10.1	**95.8**	95.1	96.3
	vomiting	**28.4**	23.0	34.2	**78.1**	76.9	79.2	**1.3**	1.1	1.6	**0.9**	0.8	1.0	**6.3**	5.0	7.8	**95.5**	94.8	96.1
	persistent vomiting	**8.9**	5.7	13.2	**96.1**	95.5	96.6	**2.3**	1.5	3.5	**0.9**	0.9	1.0	**10.3**	6.6	15.2	**95.5**	94.8	96.0
	bile-stained vomiting	**4.5**	2.2	7.8	**98.9**	98.6	99.2	**4.1**	2.2	7.8	**1.0**	0.9	1.0	**17.2**	8.9	28.7	**95.3**	94.7	95.9
	child eats and drinks less	**64.1**	58.0	69.9	**54.3**	52.9	55.7	**1.4**	1.3	1.5	**0.7**	0.6	0.8	**6.8**	5.8	7.8	**96.7**	96.0	97.3
	child pees less	**22.4**	17.4	28.1	**86.9**	86.0	87.8	**1.7**	1.4	2.2	**0.9**	0.8	1.0	**7.9**	6.0	10.2	**95.7**	95.1	96.3
	short of breath	**24.7**	19.6	30.4	**84.8**	83.7	85.8	**1.6**	1.3	2.0	**0.9**	0.8	1.0	**7.8**	6.1	9.9	**95.6**	94.9	96.2
	coughing	**61.5**	55.4	67.4	**42.5**	41.1	43.9	**1.1**	1.0	1.2	**0.9**	0.8	1.1	**5.3**	4.5	6.1	**95.5**	94.6	96.3
	headache	**8.1**	5.0	12.4	**93.3**	92.5	94.0	**1.2**	0.8	1.9	**1.0**	0.9	1.0	**5.7**	3.4	8.7	**95.3**	94.7	95.9
	neck pain	**4.2**	2.0	7.6	**98.3**	97.9	98.6	**2.5**	1.3	4.7	**1.0**	0.9	1.0	**11.0**	5.4	19.3	**95.4**	94.8	96.0
observation	gut feeling something is wrong	**43.2**	37.0	49.5	**86.8**	85.9	87.8	**3.3**	2.8	3.8	**0.7**	0.6	0.7	**14.5**	12.1	17.2	**96.7**	96.2	97.2
	clinical impression child is seriously ill	**30.6**	25.0	36.6	**93.2**	92.5	93.9	**4.5**	3.7	5.6	**0.7**	0.7	0.8	**18.7**	15.1	22.8	**96.3**	95.8	96.9
	child is irritable	**17.0**	12.6	22.1	**91.0**	90.2	91.8	**1.9**	1.4	2.5	**0.9**	0.9	1.0	**8.8**	6.5	11.7	**95.5**	94.9	96.1
	child is drowsy	**9.7**	6.4	14.0	**96.5**	95.9	97.0	**2.7**	1.8	4.1	**0.9**	0.9	1.0	**12.3**	8.1	17.6	**95.4**	94.8	96.0
	child had reduced consciousness	**0.4**	0.0	2.2	**99.6**	99.4	99.8	**1.0**	0.1	7.7	**1.0**	1.0	1.0	**5.0**	0.1	24.9	**95.2**	94.6	95.7
	child is inconsolable	**9.7**	6.4	14.0	**95.3**	94.7	95.8	**2.1**	1.4	3.0	**0.9**	0.9	1.0	**9.5**	6.2	13.7	**95.4**	94.8	95.9
	child is moaning	**12.5**	8.7	17.1	**98.2**	97.8	98.5	**6.8**	4.6	9.9	**0.9**	0.9	0.9	**25.6**	18.2	34.2	**95.7**	95.1	96.2
	child has nasal flaring	**10.1**	6.7	14.5	**97.7**	97.2	98.1	**4.3**	2.9	6.5	**0.9**	0.9	1.0	**18.1**	12.1	25.3	**95.5**	94.9	96.1
	chestwall retractions	**11.7**	8.0	16.2	**95.0**	94.4	95.6	**2.4**	1.7	3.4	**0.9**	0.9	1.0	**10.7**	7.3	14.9	**95.5**	94.9	96.0
	child laughs less	**28.9**	23.4	34.9	**89.6**	88.8	90.5	**2.8**	2.3	3.4	**0.8**	0.7	0.9	**12.4**	9.9	15.3	**96.1**	95.5	96.7

LR+: positive likelihood ratio; LR-: negative likelihood ratio; PPV: positive predictive value; NPV: negative predictive value; 95% CI: 95% confidence intervals

Appendix 3.4: bivariable analyses of clinical features to identify serious infections in specialist setting *(continued)*

type	variable	sensitivity	95% CI		specificity	95% CI		LR+	95% CI		LR-	95% CI		PPV	95% CI		NPV	95% CI	
clinical examination	pus on tonsils	**2.0**	0.6	4.5	**94.2**	93.5	94.9	**0.3**	0.1	0.8	**1.0**	1.0	1.1	**1.7**	0.6	3.9	**95.0**	94.3	95.6
	signs of acute otitis media	**12.3**	8.5	16.9	**85.0**	84.0	86.0	**0.8**	0.6	1.2	**1.0**	1.0	1.1	**4.0**	2.7	5.6	**95.0**	94.4	95.7
	bilateral otitis media	**6.7**	4.0	10.5	**93.9**	93.2	94.6	**1.1**	0.7	1.8	**1.0**	1.0	1.0	**5.3**	3.1	8.4	**95.2**	94.5	95.8
	discharging ears	**2.8**	1.1	5.7	**98.2**	97.8	98.6	**1.6**	0.7	3.4	**1.0**	1.0	1.0	**7.5**	3.1	14.7	**95.3**	94.6	95.8
	extensive cervical adenopathy	**2.3**	0.9	5.0	**97.1**	96.6	97.6	**0.8**	0.4	1.8	**1.0**	1.0	1.0	**4.0**	1.5	8.5	**95.1**	94.5	95.7
	redness and or swelling of face	**5.1**	2.7	8.5	**97.1**	96.6	97.6	**1.8**	1.0	3.1	**1.0**	1.0	1.0	**8.2**	4.5	13.7	**95.2**	94.6	95.8
	purulent conjunctivae	**3.9**	1.9	7.0	**96.4**	95.9	96.9	**1.1**	0.6	2.0	**1.0**	1.0	1.0	**5.3**	2.6	9.5	**95.1**	94.5	95.7
	bilateral purulent conjunctivae	**0.8**	0.1	2.8	**97.8**	97.4	98.2	**0.4**	0.1	1.4	**1.0**	1.0	1.0	**1.8**	0.2	6.3	**95.1**	94.4	95.6
	dyspnea	**20.9**	16.1	26.4	**91.8**	91.0	92.5	**2.6**	2.0	3.3	**0.9**	0.8	0.9	**11.6**	8.8	14.8	**95.8**	95.2	96.3
	crepitations (crackling)	**19.7**	15.0	25.1	**90.7**	89.8	91.5	**2.1**	1.6	2.7	**0.9**	0.8	0.9	**9.8**	7.4	12.7	**95.6**	95.0	96.2
	reduced breathing sounds	**12.1**	8.3	16.7	**97.1**	96.6	97.6	**4.2**	2.9	6.1	**0.9**	0.9	0.9	**17.8**	12.4	24.3	**95.6**	95.0	96.1
	rhonchi	**31.0**	25.5	37.0	**73.8**	72.5	75.0	**1.2**	1.0	1.4	**0.9**	0.9	1.0	**5.8**	4.6	7.1	**95.4**	94.7	96.0
	cyanosis	**1.6**	0.4	3.9	**99.8**	99.6	99.9	**6.5**	2.1	19.9	**1.0**	1.0	1.0	**25.0**	7.3	52.4	**95.2**	94.6	95.7
	peritoneal irritation	**4.1**	2.0	7.4	**99.6**	99.4	99.8	**11.7**	5.4	25.2	**1.0**	0.9	1.0	**37.0**	19.4	57.6	**95.4**	94.8	95.9
	petechial rash	**2.7**	1.1	5.5	**98.5**	98.2	98.9	**1.8**	0.9	4.0	**1.0**	1.0	1.0	**8.8**	3.6	17.2	**95.1**	94.5	95.7
	meningeal irritation	**3.9**	1.9	7.0	**99.7**	99.5	99.8	**13.8**	6.2	30.8	**1.0**	0.9	1.0	**41.7**	22.1	63.4	**95.2**	94.6	95.8
	reduced peripheral circulation	**7.3**	4.5	11.2	**98.4**	98.0	98.7	**4.5**	2.8	7.3	**0.9**	0.9	1.0	**19.0**	11.8	28.1	**95.3**	94.7	95.9
	pale skin	**18.1**	13.6	23.3	**95.0**	94.3	95.6	**3.6**	2.7	4.8	**0.9**	0.8	0.9	**15.7**	11.8	20.3	**95.7**	95.1	96.3
	abnormal skin turgor	**1.5**	0.4	3.9	**99.4**	99.2	99.6	**2.8**	1.0	7.8	**1.0**	1.0	1.0	**12.5**	3.5	29.0	**95.1**	94.5	95.7
	abnormal fontanel tension	**0.9**	0.1	3.1	**99.9**	99.8	100.0	**13.7**	2.3	81.7	**1.0**	1.0	1.0	**40.0**	5.3	85.3	**95.4**	94.8	96.0
	swollen limb or non weight bearing extremity	**0.5**	0.0	2.9	**98.9**	98.3	99.2	**0.5**	0.1	3.5	**1.0**	1.0	1.0	**2.4**	0.1	12.9	**95.1**	94.3	95.7
	measured temperature ≥ 39.5°C	**19.2**	14.5	24.6	**90.2**	89.2	91.1	**2.0**	1.5	2.6	**0.9**	0.8	1.0	**10.7**	8.0	13.9	**94.8**	94.1	95.5
	measured temperature ≥ 40.0°C	**6.0**	3.4	9.7	**96.0**	95.4	96.6	**1.5**	0.9	2.5	**1.0**	0.9	1.0	**8.5**	4.8	13.6	**94.3**	93.6	95.0
	highest temperature (measured or reported) ≥ 39.5°C	**62.7**	56.7	68.5	**55.6**	54.2	57.0	**1.4**	1.3	1.6	**0.7**	0.6	0.8	**7.1**	6.1	8.2	**96.5**	95.8	97.2
	highest temperature (measured or reported) ≥ 40.0°C	**43.2**	37.2	49.3	**75.1**	73.9	76.3	**1.7**	1.5	2.0	**0.8**	0.7	0.8	**8.6**	7.1	10.2	**96.1**	95.4	96.7
	breathing rate ≥ 50/min	**23.3**	14.8	33.6	**90.0**	88.3	91.6	**2.3**	1.5	3.5	**0.9**	0.8	1.0	**13.5**	8.5	20.1	**94.6**	93.2	95.8
	heart rate ≥ 150/min	**35.4**	25.9	45.8	**79.9**	77.6	82.0	**1.8**	1.3	2.4	**0.8**	0.7	0.9	**11.0**	7.8	15.1	**94.6**	93.1	95.8
	oxygen saturation ≤ 95%	**29.2**	20.8	38.9	**88.9**	87.0	90.6	**2.6**	1.9	3.7	**0.8**	0.7	0.9	**18.2**	12.7	24.9	**93.7**	92.1	95.0
	capillary refill ≥ 3 seconds	**20.1**	14.1	27.3	**91.6**	90.4	92.7	**2.4**	1.7	3.4	**0.9**	0.8	0.9	**13.6**	9.4	18.7	**94.6**	93.6	95.5

LR+: positive likelihood ratio; LR-: negative likelihood ratio; PPV: positive predictive value; NPV: negative predictive value; 95% CI: 95% confidence intervals



Appendix 3.5: Receiver-Operating-Characteristic (ROC) curves for the vital signs measurements on a continuous scale per setting.

GP: general practice; specialist setting: paediatric outpatient clinic and emergency department setting combined; circles and triangles: scatter plots in GP and specialist setting respectively; regression plot: regression plot using fractional polynomials (smooth function using flexible parameterization for continuous variables). The Area Under the Curves (AUC) values are shown for both settings (black: GP setting; grey: specialist setting) in every graph. For oxygen saturation the inverse of the absolute value was used, as lower values tend to correspond with more severe cases.

PART 2: POINT-OF-CARE TESTS

Aim

to determine the analytical accuracy of the selected POC test and its added value in diagnosing serious infections in acutely ill children.

Chapter 4.

Research question

What is the agreement of the selected point-of-care C-reactive protein test with a corresponding laboratory test in children and adults?

Published as:

Jan Y Verbakel, Bert Aertgeerts, Marieke Lemiengre, An De Sutter, Dominique M A Bullens, Frank Buntinx. Analytical accuracy and user-friendliness of the Afinion point-of-care test. ***J Clin Pathol 2014; 67(1):83-86.***

ANALYTICAL ACCURACY AND USER-FRIENDLINESS OF A POINT-OF-CARE CRP TEST.

ABSTRACT

Background: Venous blood sampling can be difficult in children in ambulatory care. A point-of-care (POC) test, provided at the bedside, presents an immediate result from a droplet of blood and is especially useful in children. We aimed to determine the analytical accuracy and user-friendliness of the Afinion CRP test in children and adults.

Methods: We performed POC CRP tests in children (1 month - 18 years) at an inpatient paediatric unit and outpatient paediatric clinic, and in adults (18 - 65 years) attending a general practice surgery. The accuracy was assessed comparing the results between the Afinion CRP test and the venous sample immunoturbidimetric CRP test on a Roche Cobas c702. The correlation was analysed and plotted using the Passing-Bablok linear regression method and the differences and agreement according to the Bland-Altman method. The participating general practitioners evaluated user-friendliness.

Results: In 100 children the agreement between the Afinion CRP test results and the Cobas CRP test results demonstrated a mean difference of 0.1% with 95% limits of agreement from -17.6% to 17.4%. A slope of 1.01 (95% CI 1.00 to 1.05) was found with a strong correlation (y=1.01x - 0.04) even at high CRP concentrations.
In the 35 adults a mean difference of 1.3% with 95% limits of agreement from -15.4% to 12.8% was found.
The GPs gave the POC CRP test median scores of 4 to 5 for all items.

Conclusions: We were able to confirm the analytical accuracy of the Afinion POC CRP test in comparison with an immunoturbidimetric CRP test on a Cobas c702 device in children as well as in adults. Even at high CRP concentrations, the test demonstrated high agreement and precise measurements. All participating physicians and the principal investigators deemed the device user-friendly.

INTRODUCTION

In children it is often essential to recognize serious infections at an early stage to reduce possible life-threatening complications.
C-reactive protein (CRP) is an acute-phase protein, secreted in response to any infection or inflammation.[1] Venous blood sampling can be difficult in children in ambulatory care. A point-of-care (POC) test, provided at the bedside, presents an immediate result from a droplet of blood and is especially useful in children.
Previous generations of POC CRP tests have shown good correlation with standard laboratory tests in studies in primary care and emergency departments.[1-3] Measuring CRP could contribute to clinical decision-making in diagnosing serious infection.[4]
We determined the analytical accuracy (closeness of the agreement between the measurement results and a reference value) and user-friendliness of the Afinion CRP test (on the Afinion AS100 Analyzer, Alere, USA), in children and adults.

METHODS

To assess analytical accuracy, we performed POC CRP tests in children (aged 1 month-18 years) admitted to an inpatient paediatric unit or attending an outpatient paediatric clinic, and in adults (aged 18-65 years) attending a general practice surgery. The participating general practitioners evaluated user-friendliness.
This study was approved by the ethical review board of the KU Leuven, under reference ML8239.

Afinion CRP test

The Afinion CRP Test Cartridge consists of a 1.5 mL glass capillary and a reagent container. The result is available within 4 min and the measuring range for CRP is 5 to 200 mg/L. One physician (JYV) performed all POC CRP tests in children, executing every fingerstick in a similar fashion (lateral side of the index finger with a small 28 Gauge spring loaded needle). For internal quality control, a positive sample provided by the device manufacturer was measured regularly to confirm the efficacy and correct performance of the test.

The accuracy was assessed comparing the results of the Afinion CRP test and the venous sample immunoturbidimetric CRP test with antibody-carrying latex particles tested performed on a Cobas c702 (Roche Diagnostics, Switzerland), the available accredited reference standard test at the university hospital central laboratory.

The correlation was analysed and plotted using the Passing-Bablok linear regression method and the differences and agreement according to the Bland-Altman method.

In three general practice surgeries, 10 physicians performed POC CRP tests. They were asked to fill out a questionnaire, consisting of a 5-point Likert scale, based on device start-up, handling of the capillary, filling of the capillary, placing the capillary in the cartridge, placing the test cartridge in the test device, duration of analysis and display of results.

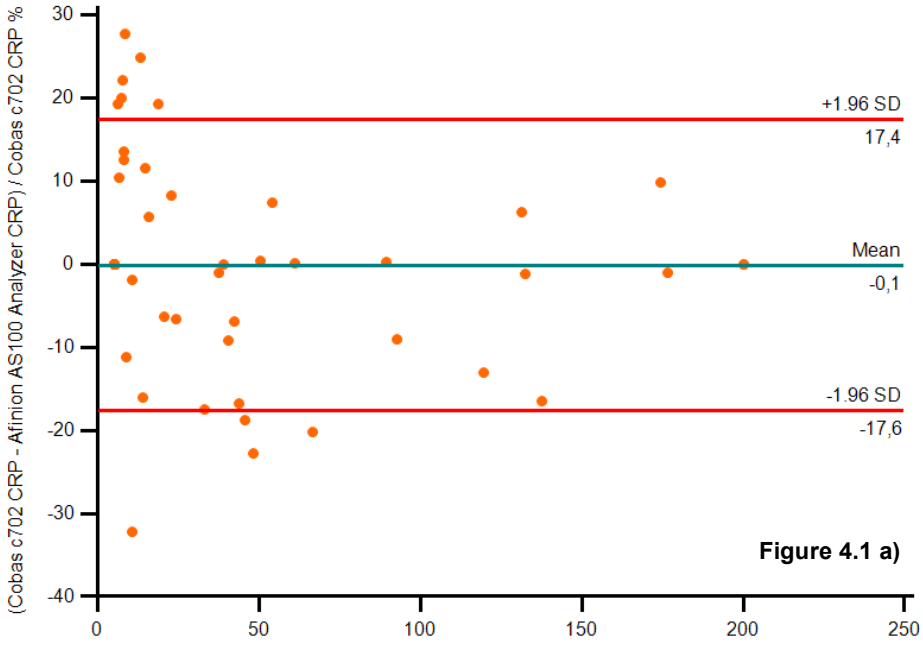
RESULTS

From May to June 2012, 100 children (56% boys) at a median age of 9.9 years (IQR 4.7-14.5) were tested and 35 adults (54% men) at a median age of 35.5 (IQR 29.3-45.6).

In children aged 0-18 years
Figure 4.1a illustrates the agreement on a Bland-Altman-plot in 100 children between the CRP test results on the Afinion AS100 Analyzer and the CRP test results on the Cobas c702 with a mean difference of 0.1% with 95% limits of agreement from -17.6% to 17.4% with all differences below ±23 mg/L. (**Figure 4.2a**)
A slope of 1.01 (95% CI 1.00 to 1.05) was found with a regression equation of y=1.01x - 0.04, indicating a strong correlation even at high CRP concentrations. (**Figure 4.3a**)

In adults aged 18-65 years
Figure 4.1b shows a mean difference of 1.3% with 95% limits of agreement from -15.4% to 12.8% in the 35 adults with all differences below ±4 mg/L. (**Figure 4.2b**)
A slope of 1.02 (95% CI 1.01 to 1.08) with a regression equation of y=1.02x - 0.10 was found. (**Figure 4.3b**)

User-friendliness of the POC CRP device
The results of the survey provided median scores of 4 to 5 for all items evaluated.



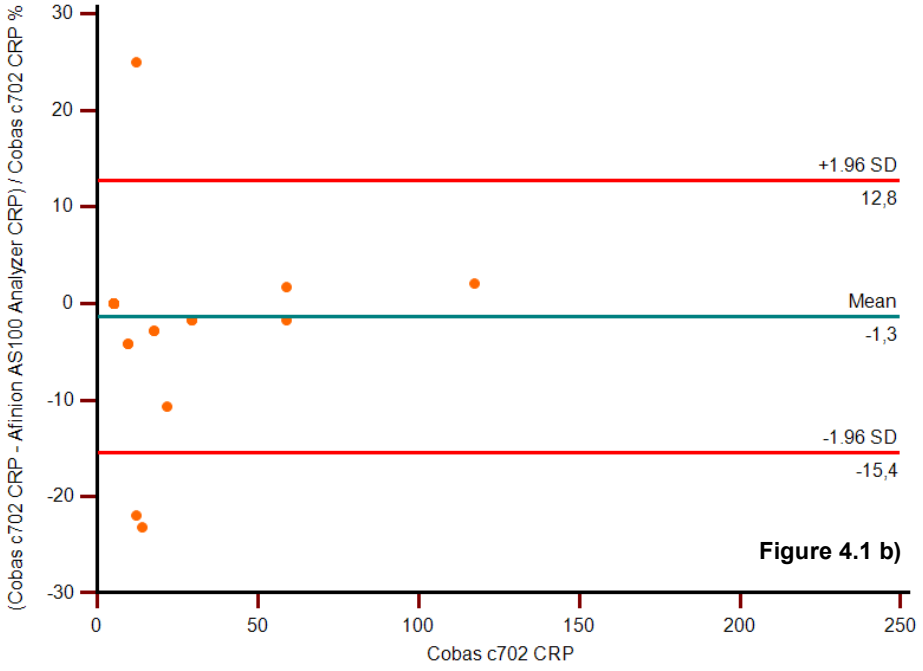
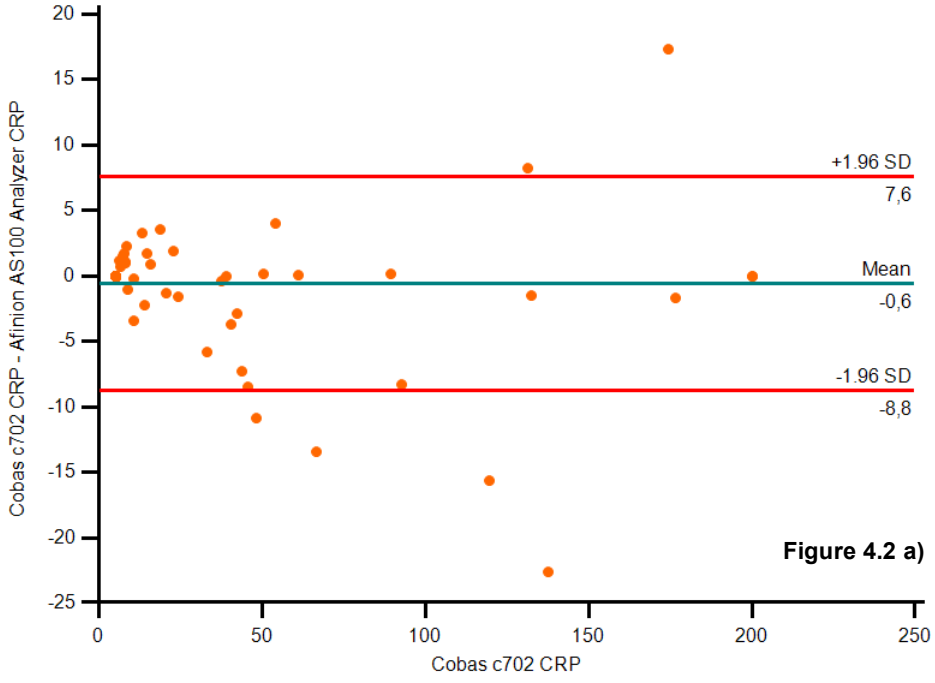


Figure 4.1: (a) Percentage difference plot of the agreement between the Afinion point-of-care (POC) CRP test results on an AS100 Analyzer and the CRP test results on a Roche Cobas c702 in 100 children. (b) Percentage difference plot of the agreement between the Afinion POC CRP test results on an AS100 Analyzer and the CRP test results on a Roche Cobas c702 in 35 adults.
CRP: C-reactive protein; dots: scatter; central line: mean agreement between both methods; outer lines: 95% limits of agreement; SD: standard deviation.



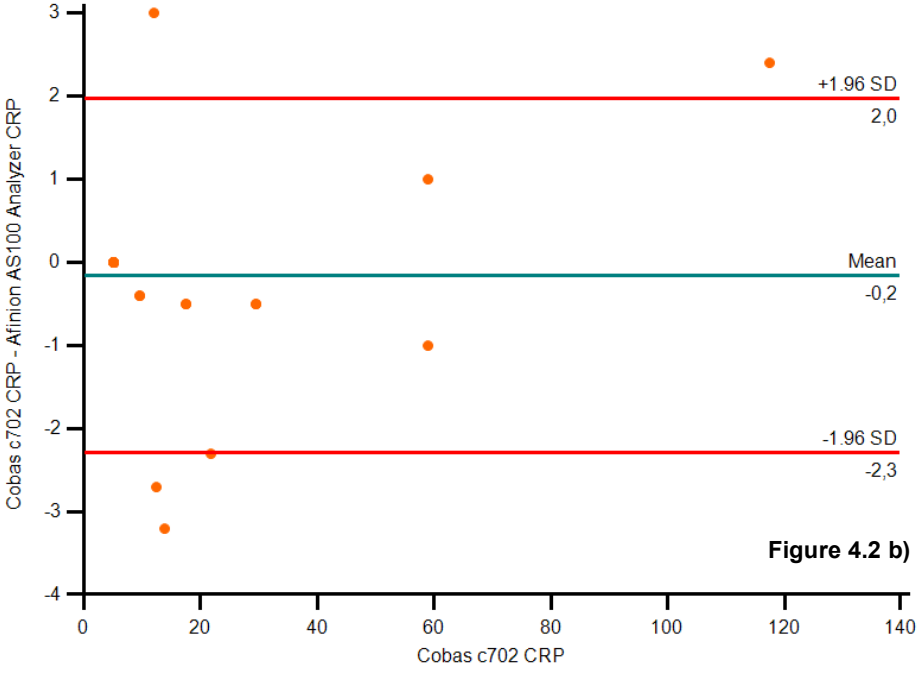


Figure 4.2: (a) Absolute difference plot of the agreement between the Afinion point-of-care (POC) CRP test results on an AS100 Analyzer and the CRP test results on a Roche Cobas c702 in 100 children. (b) Absolute difference plot of the agreement between the Afinion POC CRP test results on an AS100 Analyzer and the CRP test results on a Roche Cobas c702 in 35 adults.
CRP: C-reactive protein; dots: scatter; central line: mean agreement between both methods; outer lines: 95% limits of agreement; SD: standard deviation.

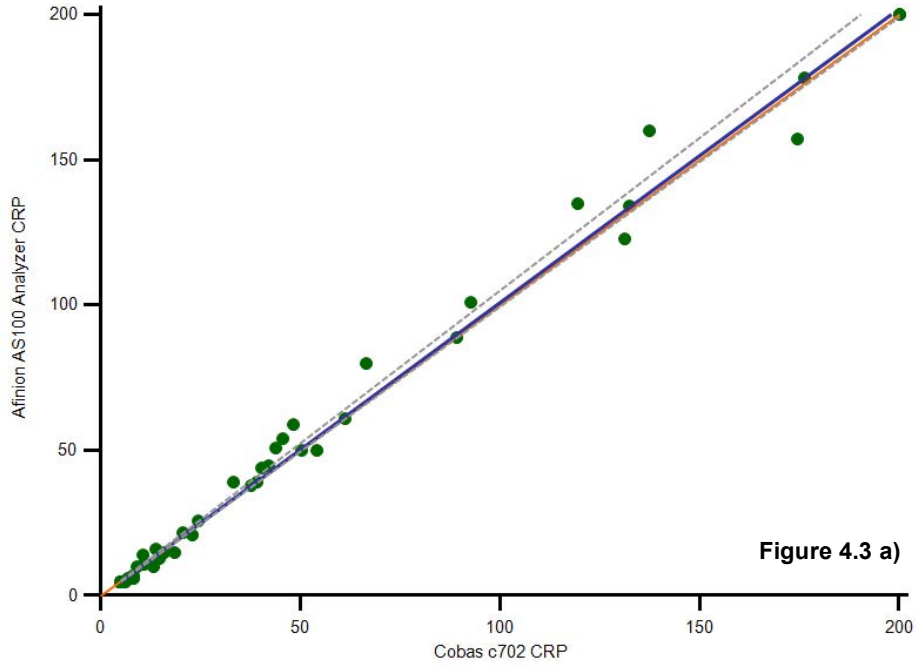


Figure 4.3 a)

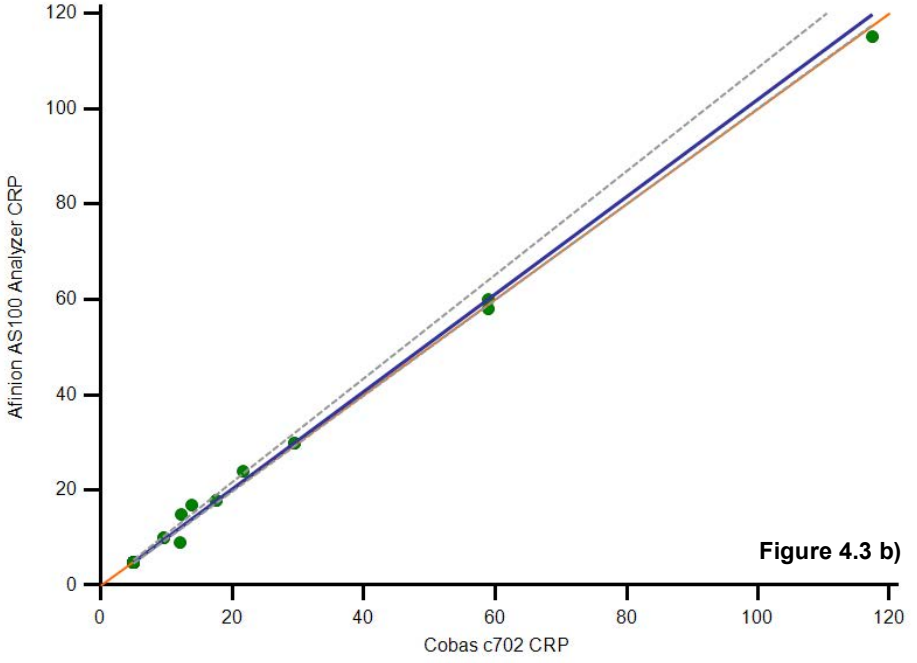


Figure 4.3 b)

Figure 4.3: (a) scatter plots of the Afinion point-of-care (POC) CRP test results on an AS100 Analyzer and the CRP test results on a Roche Cobas c702 in 100 children, fitted with a regression line. (b) scatter plots of the Afinion POC CRP test results on an AS100 Analyzer and the CRP test results on a Roche Cobas c702 in 35 adults, fitted with a regression line. CRP: C-reactive protein; dots: scatter; grey dashed line: 95% confidence intervals of regression; for comparison the line y=x is presented depicting perfect agreement.

DISCUSSION

We were able to confirm the analytical accuracy of the Afinion POC CRP test in comparison with an immunoturbidimetric CRP test on a Cobas c702 device in children as well as in adults. Even at high CRP concentrations, the test demonstrated high agreement and precise measurements. The few differences between both methods in cases with high CRP levels were not found to be clinically significant, as they would not change decisions on further treatment or testing. All participating physicians and the principal investigators deemed the device user-friendly.

This is the first study to examine the Afinion CRP test in children. We performed capillary blood CRP tests in a large sample of 100 children. A total of 100 of the 104 children (and their parents) eligible for inclusion were willing to participate, ensuring a representative sample of those children admitted to hospital or attending a paediatric clinic. Although we provided a sufficiently large sample of children, generalizability to other settings (e.g. primary care) and populations (e.g. neonates) cannot be guaranteed.

As this is the first study to evaluate the Afinion CRP test, we can only compare these findings with those of the Nycocard, its predecessor. Previous studies have confirmed its use to be acceptable in children.[5-8] It, however, required additional steps such as dilution of the sample, applying a conjugate, washing the sample and finally reading the test result. We believe the Afinion CRP Analyzer to be undeniably user-friendlier as confirmed by our results.

Diagnostic accuracy studies are needed to evaluate the added value of POC CRP tests in diagnosing serious infections in children. The selected device met primary requirements to assess an acutely ill child at risk of a serious infection. Further research is needed to support this assumption.

CONCLUSION

In this study, the Afinion AS100 Analyzer was accurate in children and should be considered reliable and user-friendly.

ACKNOWLEDGEMENTS

We would like to thank Professor Dr. Christel Van Geet, Professor Dr. François Vermeulen, the nursing staff of wards 302 and 341 of the Department of Paediatrics, University Hospitals Leuven and all participating physicians for contribution to the study and data collection. We would like to thank Professor Flor Vanstapel and Professor Els Dequeker for their advice on POC testing and laboratory testing of CRP. We would also like to thank Alere Health, Belgium, for providing the POC devices and the technical support. We would like to thank all the children and parents who participated in this study.

COMPETING INTERESTS

DMAB is a recipient of a senior clinical investigator fellowship from the Research Foundation - Flanders (FWO).

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Chapter 5.

Research question

What is the diagnostic value of the selected point-of-care test together with vital signs and symptoms in diagnosing serious infections in acutely ill children in ambulatory care?

Protocol published as:

Jan Y Verbakel, Marieke B Lemiengre, Tine De Burghgraeve, An De Sutter, Dominique M A Bullens, Bert Aertgeerts, Frank Buntinx, on behalf of the ERNIE 2 collaboration. Diagnosing serious infections in acutely ill children in ambulatory care (ERNIE 2 study protocol part A): diagnostic accuracy of a Clinical Decision Tree and added value of a Point-of-Care C-reactive protein Test and Oxygen Saturation. ***BMC Pediatr 2014, 14:207.***

and:

Marieke B Lemiengre, Jan Y Verbakel, Tine De Burghgraeve, Bert Aertgeerts, Frans De Baets, Frank Buntinx, An De Sutter, on behalf of the ERNIE2 collaboration. Optimizing antibiotic prescribing for acutely ill children in primary care (ERNIE2 study protocol, part B): a cluster randomized, factorial controlled trial evaluating the effect of a Point-of-Care C-reactive protein test and a brief intervention combined with written safety net advice. ***BMC Pediatr 2014, 14:246.***

DIAGNOSING SERIOUS INFECTIONS IN ACUTELY ILL CHILDREN IN AMBULATORY CARE: ADDED VALUE OF A POINT-OF-CARE C-REACTIVE PROTEIN TEST.

ABSTRACT

Background: Acute infection is the most common presentation of children to ambulatory care. In contrast, serious infections are rare and often present at an early stage. To avoid complications or death, early recognition and adequate referral are essential. In a recent large study children were included prospectively to construct a symptom-based decision tree with a sensitivity and negative predictive value of nearly 100%. To reduce the number of false positives, point-of-care tests might be useful, providing an immediate result at the bedside. The most probable candidate is C-reactive protein.

Methods: This is a diagnostic accuracy study of signs, symptoms and point-of-care tests for serious infections. Acutely ill children presenting to a general practitioner or paediatrician were included consecutively in Flanders, Belgium. Children testing positive on the decision tree received a point-of-care C-reactive protein test. The outcome of interest was hospital admission more than 24 hours with a serious infection within 5 days. We reported the diagnostic accuracy of the decision tree + the point-of-care C-reactive protein test result in sensitivity, specificity, likelihood ratios and predictive values. Considering suboptimal performance in specialist setting, we explored whether a new decision tree could be constructed, feeding only clinical features to the model that could be assessed by trained triage nurses and junior doctors.

Results: Adding the results of the point-of-care C-reactive protein test to the decision tree increased the specificity from 83.6% (95% CI 82.3-84.9%) to 89.5% (95%CI 88.3 - 90.5%) while maintaining a sensitivity of 100% (95% CI 71.5 - 100%) in the GP setting. The newly developed multivariable model in the specialist setting achieved a sensitivity of 97.1% (95% CI 94.3-98.7%) and a negative predictive value of 99.6% (95% CI 99.2-99.8%).

Conclusions: Adding point-of-care C-reactive protein test results to a validated signs and symptoms-based decision tree aids identifying serious infections in the GP setting and can potentially reduce the number of investigations and admissions in children with non-serious infections. We propose a new multivariable model to be used as a triage instrument in specialist settings to safely rule out serious infections.

BACKGROUND

The 4-step decision tree was able to identify all children with a serious infection in the GP setting. However, the specificity of 78% means that a substantial proportion of children (22%) will have a false positive result, potentially leading to an increase in onward referrals or additional testing.

Adding a C-reactive protein (CRP) test may rule out a serious infection in those testing positive to the decision tree thus reducing false positive rates. In the paediatric outpatient and emergency department (ED) setting, where a considerable amount of first contact consultations in acutely ill children are assessed, adding CRP to the decision tree might increase its diagnostic performance both in terms of sensitivity and specificity.

Moreover, a decision tree consisting of history features and a CRP, which is assessable by a trained triage nurse or junior doctor, could be a cost-effective way of managing acutely ill children in a specialist setting.

Point-of-care (POC) tests are defined as laboratory and other tests performed at the patient's bedside (or in the doctor's surgery for ambulatory care). The physician obtains an immediate result and management can be adjusted accordingly. This makes them especially attractive in situations where a fast decision is warranted, such as urgent-access ambulatory care. Typically, POC tests are minimally invasive, and thus applicable in acute paediatric care.

An earlier systematic review identified CRP and procalcitonin as the best performing laboratory tests to detect serious infections in febrile children in ambulatory settings.[1, 2] Despite these promising results, evidence is inconclusive because most studies were performed in secondary care settings. In addition, their use was limited because they required a normal blood sample to be sent off to the laboratory and results would become available too late to influence clinical management. At present, there is only one POC test for procalcitonin[3] which takes 30 minutes to produce a result and requires blood centrifugation, making it unsuitable for use in acute ambulatory care, especially in general practice where consultations last between 10-15 minutes. On the other hand, a fast and accurate POC test for CRP is available that produces a result within 4 minutes. (see **Chapter 4**)

In this study, we aim to explore the added value of a POC CRP test following a positive result on a 4-step decision tree in diagnosing serious infection in acutely ill children in ambulatory care.

METHODS

Design

This is a prospective diagnostic accuracy study in ambulatory care (defined as general practice, paediatric outpatient clinics or EDs) identifying the diagnostic value of a POC CRP test for serious infection. The main outcome measure was a serious infection for which a hospital admission for at least 24 hours was required within 5 days of first contact.

Participants, Outcome measure & Sample Size calculation

Details concerning the participants, outcome measure verification and sample size calculation are described in full detail in **Chapter 3**. In short, we recruited children aged 1 month to 16 years who presented with an acute illness to general practice, ambulatory paediatric care or ED. The target condition was hospital admission (for more than 24 hours) for a serious infection, defined as sepsis (including bacteraemia), meningitis, appendicitis, pneumonia, osteomyelitis, cellulitis, bacterial gastro-enteritis with dehydration, complicated urinary tract infection, each verified by their corresponding reference standard test.

Index tests

4-step Decision Tree

As part of a thorough clinical assessment, physicians were asked to score the 4-step decision tree, as developed by Van den Bruel et al.[4]. Children testing positive on this tree then proceeded to a POC CRP test.

POC CRP test (fingerstick)

Based on sample volume, test duration, accuracy and user-friendliness, we selected the Afinion™ CRP Test Cartridge, which consists of a 1.5 µL glass capillary to be filled with blood from a fingerstick and a reagent container. It requires no handling of the sample. The result is available within 4 minutes. The CRP measuring range is 5 - 200 mg/L.

We trained all physicians on how to perform the POC CRP test, as they were not blinded from the final result. For internal quality control, a low and a high control positive sample was tested at regular intervals to confirm the efficacy and correct performance of the test according to the manufacturer's instructions. The device distributor provided technical assistance in case of a device malfunction.

Statistical Analysis

I. Exploratory analysis: bivariable diagnostic accuracy of POC CRP

We constructed Receiver-Operating-Characteristic (ROC) curves to assess the value of CRP for general practice and for the specialist setting (paediatric outpatient and ED setting, combined) respectively.
The accuracy of the CRP test results was analysed for our composite outcome of serious infections at different thresholds: 5 and 200 mg/L (lower and upper limit of the POC CRP test as measured with the Afinion CRP test) and 20 and 80 mg/L (identified by previous research as rule out and rule in threshold, respectively).[5] We reported the diagnostic accuracy in sensitivity, specificity, and positive and negative predictive values with their 95% confidence intervals (CI). A correction of 0.5 was added to every cell in case of an empty cell in a 2 by 2 table.

II. Primary analysis: diagnostic accuracy of the 4-step decision tree and POC CRP

For every child testing positive on the pragmatic version of the decision tree (see **Chapter 3**) with easy to remember thresholds, we added a POC CRP test to improve specificity by lowering the number of children testing false positive. We used classification and regression tree analysis (CART) to select the optimized threshold for the CRP test in this dataset. We tested whether this resulted in a statistically significant increase in sensitivity or specificity by comparing confidence intervals to those of the 4-step decision tree without CRP and in overall accuracy by testing for differences between areas under the receiver-operating characteristic (ROC) curves (AUC) using chi square (chi^2) tests.
Subgroup analyses were performed according to setting: GP, outpatient paediatric and emergency department, and according to diagnostic category: pneumonia, complicated urinary tract infections, and sepsis and meningitis.

III. Secondary analysis: developing a new decision tree for triage in specialist settings

Considering the suboptimal performance of the 4-step decision tree in ambulatory paediatric care and the ED, we explored whether a new decision tree could be constructed, deliberately only feeding clinical features to the model that could be assessed by trained triage nurses and junior doctors. As a result, analyses were limited to the POC CRP test, all items from history taking, all items from observation (including skin-related items), and none of the clinical examination items, except the vital signs measurements. (**Appendix 3.1**). This selection was based on expert opinion from a group of clinicians involved in teaching and training in acute paediatric care.

"Gut feeling something is wrong" and "clinical impression child is seriously ill" are less specific when assessed by inexperienced clinicians and are considered to be holistic features encompassing all available information obtained during a clinical examination,[6] which is why they were deemed unsuitable for this specific analysis.
We used CART analyses to develop this decision tree, limiting the minimum split size to 20 and applying a weighing factor of 100 for misclassification of serious infection. This weight was chosen in a data-driven way balancing maximum sensitivity with the complexity of the tree.
To avoid over-fitting, we performed a 50-fold cross-validation.
Sensitivity analyses were performed, comparing the results of all children versus (a) children included only once during the study period to avoid clustering based on children with a predisposition for abnormal clinical findings such as high temperature and (b) children up to 36 months of age, in accordance with previous research.[7-9]

Dealing with missing values
The median number of missing data per variable was 3.9% (range 0.0 to 32.0%) with the highest numbers for the vital signs measurements. (**Appendix 3.1**). There was 12.4% and 11.3% missing data for POC CRP in the GP and specialist setting, respectively.
We used CART analysis (except for the bivariable analysis), which avoids limiting the analysis to complete cases, which would reduce the total number of subjects, but allows for missing value categorization for categorical predictors and informative treatment of missing values for continuous predictors. We again limited the minimum split size to 20 and applied a weighing factor of 100 for misclassification of serious infection.

Whenever missing values were present for the key variables, they were treated as:
- a separate level of the variable for categorical variables
- a continuous predictor value at one of either sides of the sorted values for continuous variables, in which case the optimal split was determined by CART.

If missing values for a continuous variable were categorized on one end of the optimal split, the significance of this categorization was evaluated on clinical grounds. For example, if missing values for temperature were categorized on the high end of the temperature values, a sensitivity analysis would have been performed comparing complete case analysis to the full data analysis base on this specific split, since missing values for temperature are more likely to be associated with lower values of temperature as clinicians tend to record abnormal findings more than normal findings.

All analyses were performed with Excel (Microsoft Corporation, USA), Stata software (version 11.2; Stata Corp., College Station, TX, USA), and JMP Statistical Discovery (version Pro 11.1.1; SAS Institute Inc., NC, USA).

RESULTS

Baseline characteristics and validation results of the decision tree are described in **Chapter 3**. We obtained 8962 inclusions between February 15th 2013 and February 28th 2014. As shown in **Figure 3.2**, 8664 inclusions (corresponding to 7355 unique children) were available for analysis: 3147 inclusions in the GP setting, 2895 inclusions in the paediatric outpatient clinic setting and 2622 inclusions in the ED setting.

I. Exploratory analysis

The area under the curve (AUC) value for CRP was 0.76 (95% CI 0.73-0.79) in the specialist setting versus 0.70 (95% CI 0.57-0.84) in the GP setting, but the difference was not statistically significant. (chi^2: p=0.4342) (**Figure 5.1**)

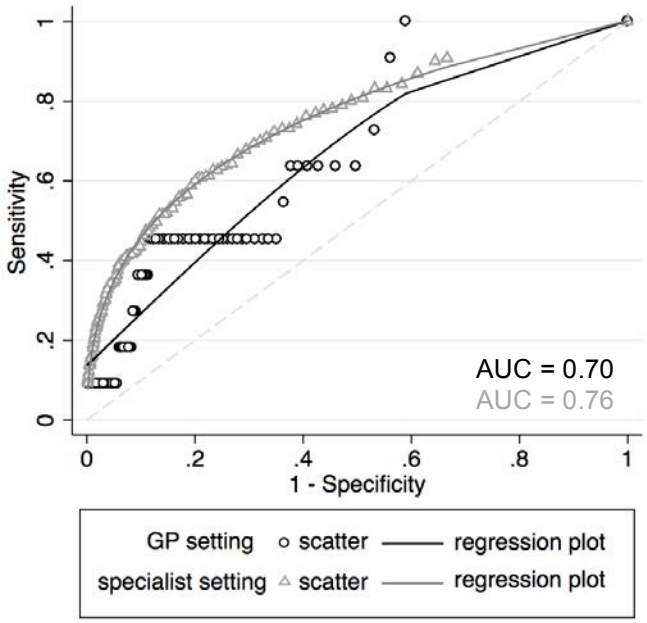

Figure 5.1: Receiver-Operating-Characteristic (ROC) curve for C-reactive protein test result (fingerstick) on a continuous scale per setting.
GP: general practice; specialist setting: paediatric outpatient clinic and emergency department setting; circles and triangles: scatter plots in each setting; regression plot: regression plot using fractional polynomials (smooth function using flexible parameterization for continuous variables). The Area Under the Curves (AUC) values are shown for both settings (black: GP setting; grey: specialist setting) in every graph.

The diagnostic accuracy of the CRP test results at different thresholds in the general practice and specialist setting (paediatric outpatient clinic and ED setting combined) is shown in **Appendix 5.1**. As expected at a low threshold of 5 mg/L, sensitivities were above 86.8% for all settings, with a sensitivity of 100% (95% CI 71.5-100%) in the GP setting, at specificities ranging from 41.1% (95% CI 39.8-42.5%) in the specialist setting to 64.1% (95% CI 62.4-65.8) in the GP setting.
At a higher threshold of 80 mg/L, sensitivities dropped below 33.5% but specificities were all above 95%.

II. Primary Analysis: added value of POC CRP

The diagnostic accuracy of the pragmatic version of the decision tree plus the POC CRP test is shown in **Table 5.1**, with subgroup analyses for the three pre-defined settings: GP, paediatric outpatient clinic and emergency department.

Table 5.1: Results of added value of POC CRP analysis in the three pre-defined settings

setting	prevalence (%) (n inclusions)		pragmatic tree for all serious infections without CRP	pragmatic tree for all serious infections with CRP
GP	0.3 (3147 inclusions)	sens	**100** (71.5 - 100)	**100** (71.5 - 100)
		spec	**83.6** (82.3 - 84.9)	**89.5** (88.3 - 90.5)
		LR+	**5.9** (5.1 - 6.8)	**9.1** (7.8 - 10.6)
		LR-	**0.0** (0.0 - 0.8)	**0.0** (0.0 - 0.7)
		PPV	**2.1** (1.1 - 3.7)	**3.2** (1.6 - 5.7)
		NPV	**100** (99.9 - 100)	**100** (99.9 - 100)
		%pos	**17**	**11**
Paed	2.8 (2944 inclusions)	sens	**93.9** (86.3 - 98.0)	**68.3** (57.1 - 78.1)
		spec	**43.9** (42.0 - 45.7)	**76.9** (75.4 - 78.5)
		LR+	**1.7** (1.6 - 1.8)	**3.0** (2.5 - 3.5)
		LR-	**0.1** (0.1 - 0.3)	**0.4** (0.3 - 0.6)
		PPV	**4.6** (3.6 - 5.7)	**7.8** (6.0 - 10.0)
		NPV	**99.6** (99.1 - 99.9)	**98.8** (98.3 - 99.2)
		%pos	**57.2**	**24.3**
ED	7.3 (2573 inclusions)	sens	**79.5** (73.0 - 85.0)	**59.5** (52.1 - 66.5)
		spec	**37.6** (35.7 - 39.6)	**74.0** (72.2 - 75.8)
		LR+	**1.3** (1.2 - 1.4)	**2.3** (2.0 - 2.6)
		LR-	**0.6** (0.4 - 0.7)	**0.6** (0.5 - 0.7)
		PPV	**9.2** (7.9 - 10.7)	**15.4** (12.9 - 18.3)
		NPV	**95.8** (94.3 - 97.0)	**95.8** (94.8 - 96.7)
		%pos	**63.6**	**28.4**

GP: general practice; Paed: paediatric outpatient clinic; ED: emergency department; prevalence; prevalence of serious infection; n inclusions: number of inclusions in each setting; with CRP: decision tree plus pragmatic CRP-thresholds; sens: sensitivity; spec: specificity; LR+: positive likelihood ratio; LR-: negative likelihood ratio; PPV: positive predictive value; NPV: negative predictive value; %pos: percentage of children testing positive; all diagnostic characteristics are given with their 95% confidence intervals.

General practice

Adding CRP at optimized thresholds in the current data of:

(a) 5 mg/L in a child for which the doctor has a gut feeling something is wrong
(b) 13 mg/L in a child with dyspnoea
(c) 201 mg/L in a child with a temperature of >40°C

resulted in a sensitivity of 100% (95% CI 71.5-100%) and specificity of 91.5% (95% CI 90.5-92.5%).

Since every child with a serious infection had a CRP level above 5 mg/L, using CRP thresholds of 5 mg/L after every positive result on the decision tree resulted in a specificity of 89.5% (95% CI 88.3-90.5%) (**Figure 5.2**), and increased the AUC of the pragmatic tree from 0.92 (without CRP) to 0.95 (with CRP; chi^2: p<0.0001).

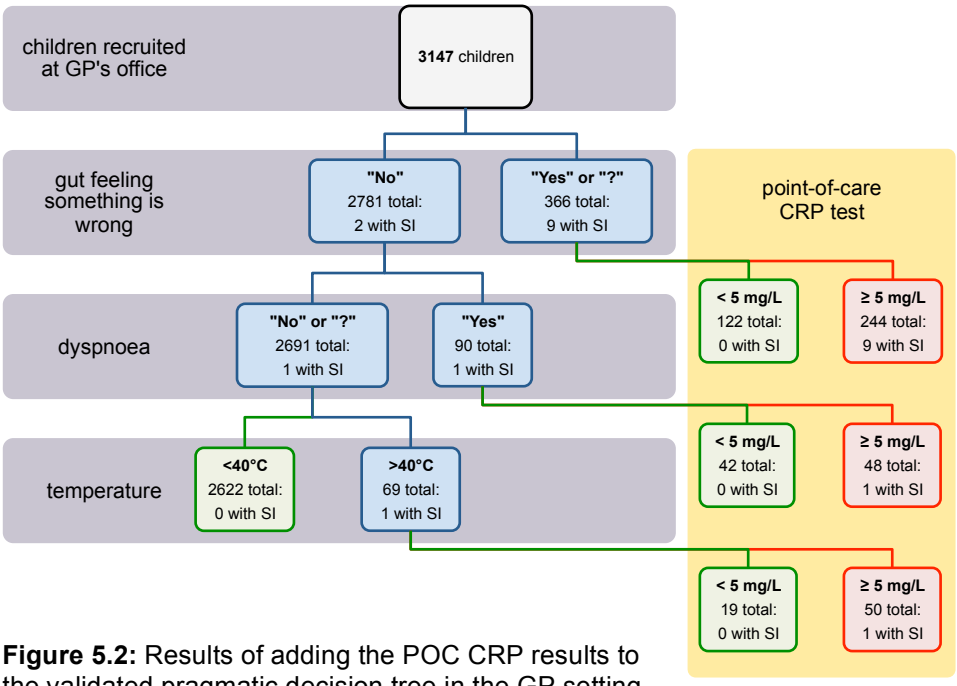

Figure 5.2: Results of adding the POC CRP results to the validated pragmatic decision tree in the GP setting
GP: general practitioner; SI: serious infections; "?": could not be evaluated

The false positive rate reduced by 52.7% from 700 to 331 children without a serious infection and still testing positive. This was equivalent to the 326 children receiving additional testing or a letter of referral from their GP. However, our decision tree identified all serious infections at first contact, while 4 of the 11 children with a serious infection were eventually not referred to hospital by their GP.

Paediatric outpatient clinic

The optimized thresholds for CRP in the current data were:

(a) 37 mg/L in a child for which the doctor has a gut feeling something is wrong
(b) 11 mg/L in a child with dyspnoea
(c) 23 mg/L in a child with a temperature of >39.5°C
(d) 20 mg/L in child aged <18 months with diarrhoea

This resulted in a sensitivity of 66.7% (95% CI 54.8-77.1%) and specificity of 79.4% (95% CI 77.9-80.9%).

Levelling all CRP thresholds to a user-friendly 20 mg/L, brought the sensitivity to 69.3% (95% CI 57.6-78.7%) and specificity to 77.1% (95% CI 75.5-78.7%), increasing the AUC of the pragmatic tree from 0.77 (without CRP) to 0.82 (with CRP; chi^2: p=0.0069), with 23 out of 75 children testing false negative. (**Figure 5.3**)

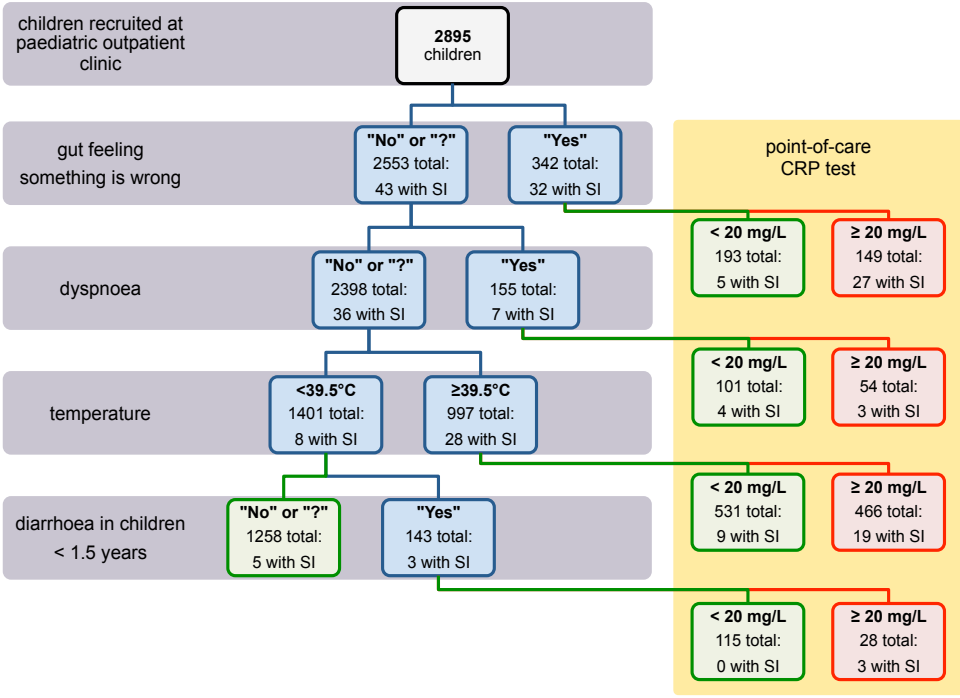

Figure 5.3: Results of adding the POC CRP results to the validated pragmatic 4-step decision tree in the paediatric outpatient setting
SI: serious infections; "?": could not be evaluated

Emergency department

In the ED setting, the optimized thresholds for CRP in the current data were:

(a) 36 mg/L in a child for which the doctor has a gut feeling something is wrong
(b) 22 mg/L in a child with dyspnoea
(c) 17 mg/L in a child with a temperature of >39.5°C
(d) 23 mg/L in a child aged <36 months with diarrhoea

leading to a sensitivity of 56.9% (95% CI 49.6-63.9%) and specificity of 74.7% (95% CI 72.9-76.4%).

When we used CRP-thresholds of 20 mg/L, this resulted in a sensitivity of 59.4% (95% CI 52.2-66.3%) and specificity of 73.8% (95% CI 72.0-75.6%), increasing the AUC of the pragmatic tree from 0.69 (without CRP) to 0.73 (with CRP; chi^2: p=0.0086), with 635 children testing false positive but more importantly 80 (40.6%) missed serious infections. (**Figure 5.4**)

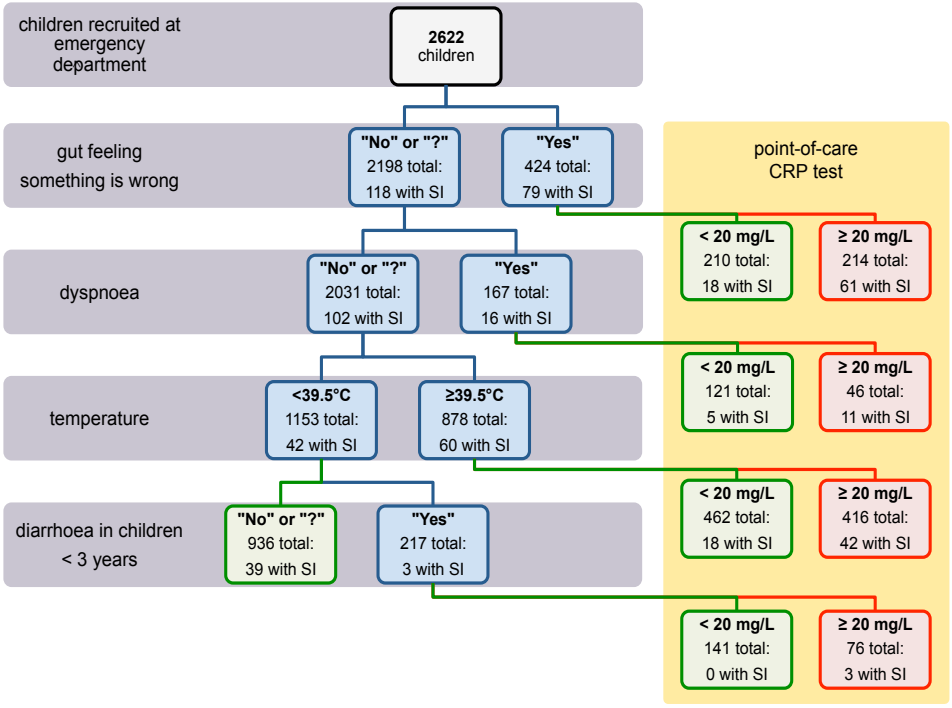

Figure 5.4: Results of adding the POC CRP results to the validated pragmatic 4-step decision tree in the emergency department setting
SI: serious infections; "?": could not be evaluated

Subgroup analyses for different outcome categories

Table 5.2 shows the subgroup analyses for pneumonia, complicated urinary tract infection and sepsis or meningitis in the three pre-defined settings.

For pneumonia, the diagnostic characteristics were almost identical to those for the composite outcome of serious infections. This is probably due to the high proportion of pneumonia cases (58% of all serious infections).

Adding CRP at a threshold of 5 mg/L (GP) or 20 mg/L (specialist setting) to the 4-step decision tree increased specificity in the GP setting for complicated urinary tract infection from 88.5% to 92.3% (95% CI 91.3-93.2%). For sepsis and meningitis, adding CRP increased specificity from 42.6% up to 73.5% (95% CI 71.8-75.1) in the specialist settings.

Table 5.2: Results of added value of POC CRP in the different outcome categories

setting		subgroups of serious infection		
		pneumonia	UTI	sepsis/meningitis
GP	sens	**100** (63.1 - 100)	**100** (15.8 - 100)	no cases
	spec	**89.4** (88.2 - 90.4)	**92.3** (91.3 - 93.2)	
	LR+	**8.9** (7.4 - 10.7)	**10.8** (6.4 - 18.2)	
	LR-	**0.1** (0.0 - 0.9)	**0.2** (0.0 - 2.3)	
	PPV	**2.3** (1.0 - 4.6)	**0.8** (0.1 - 2.9)	
	NPV	**100** (99.9 - 100)	**100** (99.9 - 100)	
Paed	sens	**64.7** (50.1 - 77.6)	**80.0** (51.9 - 95.7)	**75** (19.4 - 99.4)
	spec	**76.7** (75.1 - 78.2)	**72.7** (71.0 - 74.3)	**73.5** (71.8 - 75.1)
	LR+	**2.8** (2.2 - 3.4)	**2.9** (2.3 - 3.8)	**2.8** (1.6 - 5.0)
	LR-	**0.5** (0.3 - 0.7)	**0.3** (0.1 - 0.8)	**0.3** (0.1 - 1.9)
	PPV	**4.7** (3.3 - 6.6)	**1.5** (0.8 - 2.6)	**0.4** (0.1 - 1.1)
	NPV	**99.2** (98.7 - 99.5)	**99.9** (99.6 - 100)	**100** (99.7 - 100)
ED	sens	**66.3** (56.4 - 75.3)	**54.1** (36.9 - 70.5)	**34.8** (16.4 - 57.3)
	spec	**72.9** (71.1 - 74.6)	**74.9** (73.2 - 76.6)	**59.4** (57.5 - 61.3)
	LR+	**2.5** (2.1 - 2.8)	**2.2** (1.6 - 2.9)	**0.9** (0.5 - 1.5)
	LR-	**0.5** (0.4 - 0.6)	**0.6** (0.4 - 0.9)	**1.1** (0.8 - 1.5)
	PPV	**9.2** (7.2 - 11.5)	**3.0** (1.8 - 4.6)	**0.8** (0.3 - 1.5)
	NPV	**98.1** (97.4 - 98.7)	**99.1** (98.6 - 99.5)	**99.0** (98.4 - 99.5)

GP: general practice; Paed: paediatric outpatient clinic; ED: emergency department; sens: sensitivity; spec: specificity; LR+: positive likelihood ratio; LR-: negative likelihood ratio; PPV: positive predictive value; NPV: negative predictive value; all diagnostic characteristics are given with their corresponding 95% confidence intervals in brackets; UTI: complicated urinary tract infections; sepsis/meningitis: composite group of sepsis and meningitis cases. For these diagnostic categories subgroup analyses the pragmatic CRP-thresholds were used.

III. Secondary analysis

Newly developed decision tree

In the specialist setting, we were able to construct a new decision tree based on a pre-selected group of clinical features, as described above, to be used in paediatric outpatient clinics and the ED in children 1 month to 16 years of age.
The decision tree starts with a POC CRP test, using 2 different thresholds of 20 mg/L and 74 mg/L.

Children with a CRP level higher than 74 mg/L should be considered at high risk of a serious infection and no further splits were attempted (378 children tested positive with 100 serious infections identified (PPV of 26.5%)).
In the group of children having a CRP test result between 20 mg/L and 74 mg/L, 1065 children tested positive to any of the following seven features (different illness, no improvement with antipyretics, age <6 months, fever duration <1 day, vomiting, excessive crying, decreased eating or drinking) identifying 86 children of the 88 with a serious infection in this group.
In children testing CRP below 20 mg/L, 2071 children tested positive on the vital signs measurements (temperature, respiratory rate, heart rate, oxygen saturation and capillary refill time) and seven alarm signs (moaning, belly ache, pale skin, neck pain, petechial rash, inconsolable, drowsiness) identifying 78 of the 84 children with a serious infection in this group. (**Figure 5.5**) Although other alarm signs (e.g. reduced consciousness) could be considered important clinical features, they did not contribute to the model, due to interactions with the final decision tree predictors.

The decision tree had a sensitivity of 97.1% (95% CI 94.3-98.7%) and a negative predictive value of 99.6% (95% CI 99.2-99.8%) at a prevalence of 4.9% (95% CI 4.4-5.5%).
Our new decision tree misclassified 8 cases of serious infection: 6 children with bronchopneumonia (chest X-ray with peribronchitis and a possible pulmonary infiltrate) and 2 children diagnosed with a minor complicated urinary tract infection (a DMSA (dimercaptosuccinic acid) scan during hospital admission could not confirm pyelonephritis).

Adjusting the high level POC CRP test result threshold to a pragmatic 75 mg/L (**Figure 5.5**) did not change the diagnostic characteristics. The sensitivity analyses revealed similar sensitivities (96.5-97.1%) and negative predictive values (99.5-99.6%) with overlapping confidence intervals in the 4595 (83.3%) children in the specialist setting included only once during the study period and the 4107 (74.4%) children up to 36 months of age.

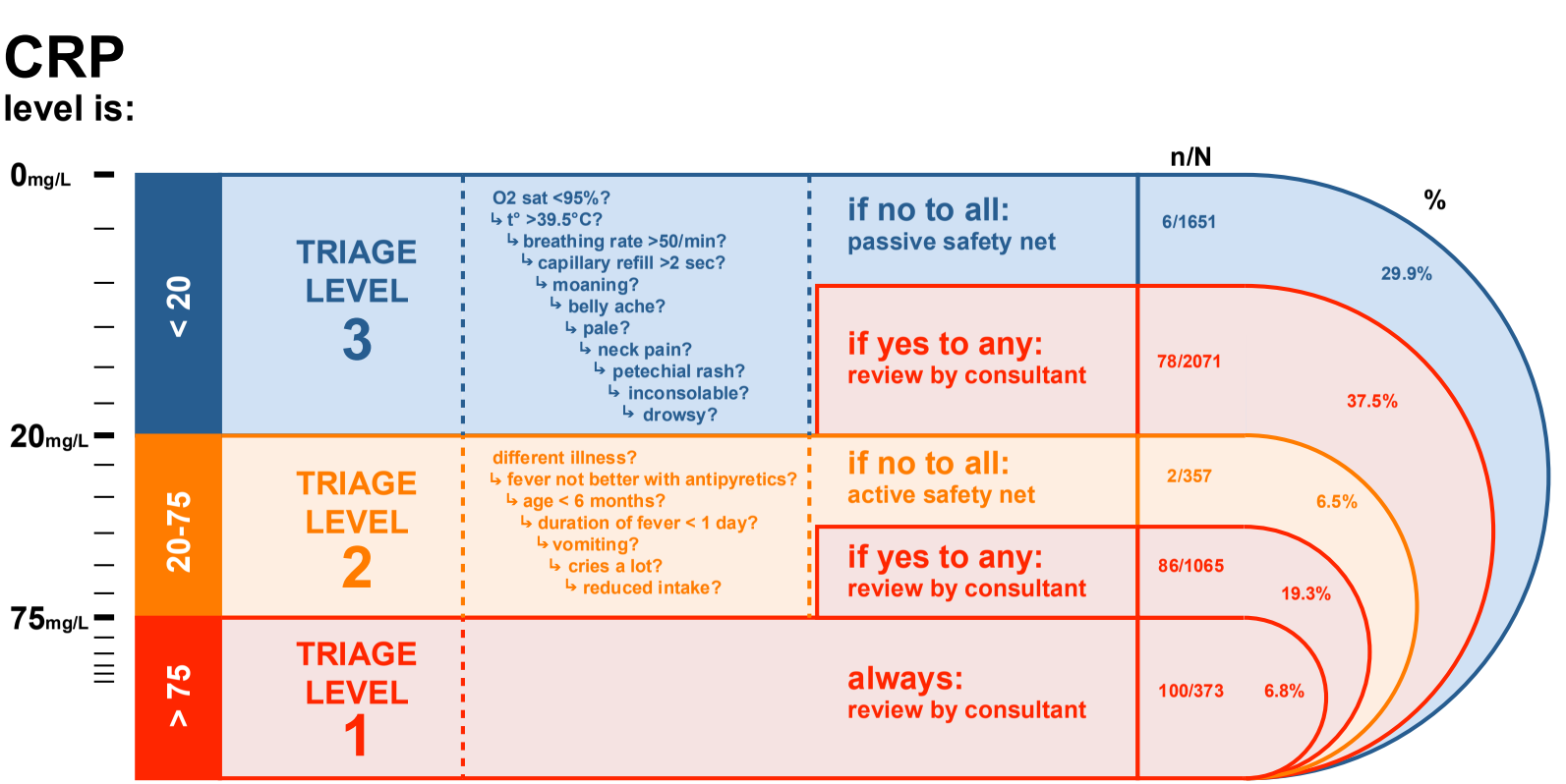

Figure 5.5: Newly developed decision tree based on clinical features in children 1 month to 16 years, assessable by trained triage nurses and junior doctors at the emergency department or paediatric outpatient clinic

CRP: C-reactive protein; "O_2 sat": oxygen saturation; "t°": temperature; "sec": seconds; "n/N": number of serious infections / number of children testing "no to all" or "yes to any"; %: percentage of all children within this category

DISCUSSION

Main findings

A threshold of 5 mg/L for the point-of-care (POC) CRP test results as a single test in the GP setting had a perfect sensitivity but low specificity. Adding CRP to the positive results on the 4-step decision tree resulted in a 100% sensitivity, at a specificity of 90% reducing the number of false positives by 53% as compared to the original 4-step decision tree without CRP testing.
Adding CRP to the 4-step decision tree resulted in an even higher specificity of 92% to diagnose children with a complicated UTI.

In the specialist settings, adding a POC CRP test to the validated decision trees was not useful, considering the poor accuracy of the tree (see **Chapter 3**). Instead, we chose to explore and suggest a new decision tree, useful in this setting, allowing junior doctors and trained triage nurses to efficiently rule out serious infections in 36% of children (1 month to 16 years) presenting to the outpatient clinic or emergency department, based on two POC CRP thresholds, and adding easy-to-assess clinical features.

Strengths and limitations

To our knowledge, this is the first large-scale trial, investigating the (added) value of POC CRP in addition to clinical features in identifying serious infections in acutely ill children in ambulatory care, including general practice, paediatric outpatient clinics and hospital emergency departments.

Verification of our target condition relied on the quality of hospital records and information obtained during follow-up. Although it is possible that not every child with a serious infection was identified, it is reasonable to assume that our strategies are robust and this was probably avoided.

Measuring the clinical signs and POC CRP (without blinding) might have led to additional testing and potentially to a diagnosis of a serious infection (verification bias), potentially increasing the sensitivity and specificity.[10]

Using a follow up of 5 days for verification of our outcome measure might seem arbitrary. If we compared the results of the POC CRP levels in our study to the variable “duration of fever” (as a proxy for the duration of illness), we observed a clear drop in CRP levels after day 5, suggesting CRP can only predict serious infections within a 5-day time frame. (**Appendix 5.2**)

Furthermore, there is evidence suggesting that different thresholds for CRP values should be applied in relation to duration of fever.[11]

Comparison with existing literature

Limited evidence on the value of laboratory tests in children in the ambulatory setting is available, none of which was obtained in primary care.[12]

A systematic review based on studies from specialist settings suggested that CRP levels <20 mg/L provided the best rule out value for serious infections in children, which is identical to the threshold identified in our analyses.[7]

Implications for clinicians

None of the suggested algorithms had both perfect sensitivity and specificity. Although perfect at ruling out serious infection in the GP setting, still 10.5% of all children (n=331) recruited, tested false positive, requiring additional testing (urinalysis, chest X-ray) or referral to hospital. This was equivalent to the 326 children (10.4%) receiving additional testing or a letter of referral from their GP in this study. However, our decision tree identified all serious infections at first contact, while 4 of the 11 children with a serious infection were eventually not referred to hospital by their GP.

The decision to refer to hospital should remain in the hands of the treating physician. We can only advise which clinical features and tests can identify all serious infections at first contact without increasing the number of unnecessary referrals or additional testing.

Although no cases of serious infections were missed in these analyses, clinical judgement should still prevail, especially if clinical uncertainty remains even after a negative test result on the decision tree. A low CRP threshold allows clinicians to reduce the number of children without a serious infection deemed at high risk based on symptoms alone. As long as appropriate (pro-)active safety netting strategies (e.g. re-consultation, telephone follow up) are installed to cope with potentially avoidable referrals or additional testing, this decision tree with POC CRP is ready for implementation in general practice.

Still 8 out of 272 serious infections, although made up of minor infections (peribronchitis and minor complicated urinary tract infection), were missed by the newly developed decision tree in the specialist settings. An appropriate strategy is required to deal with children scored as probably not having a serious infection by this model.

In children with a CRP threshold above 75 mg/L, we suggest a paediatric consultant or emergency physician should re-assess all of these children, applying appropriate ruling in strategies through additional testing available at the hospital and reassuring parents if further testing remains negative. Children with a CRP test result between 20 and 75 mg/L and “yes” to any of the sequential questions in the decision tree, should be seen by a consultant, and if “no” to all questions, we advise to install a pro-active safety net by having parents re-visit the hospital within a desirable time frame, e.g. 24 hours. Children with a CRP test result below 20 mg/L can be discharged safely if parents are advised when and how to seek further help if certain alarm signs are present in their acutely ill child (passive safety net). (**Figure 5.5**) In contrast to the GP setting, this decision tree starts off with two CRP thresholds, adding in assessment of clinical features depending on the CRP level. This is a deterministic approach and requires appropriate safety measures to be put in place to avoid decision-making on the CRP level alone.

Our newly developed decision tree focuses on a broad composite outcome of serious infections, instead of limiting detection to one specific outcome. This is especially relevant in children who initially present with generic symptoms potentially leading to different final diagnoses.
Our newly developed decision tree contains several predictors (and thresholds) similar to the NICE guideline on feverish illness in children.[13] However, we advise future updates should also include POC CRP testing, as well as parental concern and effect of antipyretics. Our analyses suggest focussing triage in specialist settings on predictors measureable by junior doctors or trained triage nurses, optimizing consultants’ time allocation.

Future research
Although our newly developed multivariable triage instrument is one of the very few based on existing recent research,[13-17] rather than expert consensus, it should be validated prospectively in a new but similar specialist paediatric population. Validating and improving a clinical prediction rule should prepare the algorithm for impact analysis and further dissemination.[18] We believe we have met these requirements by means of a pragmatic approach throughout our analyses of the 4-step decision tree, ensuring the components of the clinical prediction rule to be clinically sensible, comprehensible and appropriate for the purpose of the rule.

Further research should focus on the implementation of this validated model in combination with POC CRP and evaluate the cost-effectiveness of applying such an algorithm in terms of healthcare expenditures (e.g. avoidable admissions, costs per test and quality control of the POC devices).

ACKNOWLEDGEMENTS

We would like to thank all participating GPs and paediatricians. We would like to thank Frederick Albert, Greet Delvou and Annelien Poppe for daily follow up during the study. We would like to thank Alere Health, Belgium, for the technical support of the POC CRP devices. We would like to thank IKEA, Belgium, for the finger puppets, provided during this study. And last but not least, we would like to thank all children and parents who took part in this study.

FUNDING

This study was funded by the National Institute for Health and Disability Insurance (RIZIV, Belgium) ref. CGV n° 2012/235 and the Research Foundation - Flanders (FWO) ref. n° G067509N.

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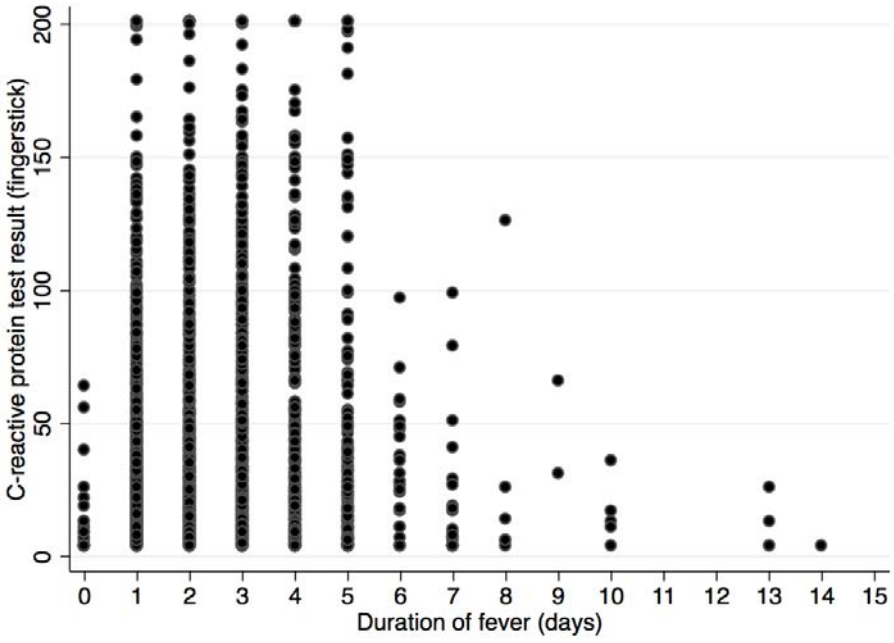
Appendix 5.1: bivariable analyses of C-reactive protein at different thresholds in both the GP and specialist setting

setting	cut-off used	**sensitivity**	95% CI		**specificity**	95% CI		**LR+**	95% CI		**LR-**	95% CI		**PPV**	95% CI		**NPV**	95% CI	
GP																			
	CRP value fingerstick ≥ 5 mg/L	**100.0**	71.5	100.0	**64.1**	62.4	65.8	**2.7**	2.4	3.0	**0.1**	0.0	1.0	**1.0**	0.5	1.7	**100.0**	99.8	100.0
	CRP value fingerstick ≥ 20 mg/L	**45.5**	16.7	76.6	**82.5**	81.1	83.8	**2.6**	1.4	5.0	**0.7**	0.4	1.1	**0.9**	0.3	2.1	**99.8**	99.5	99.9
	CRP value fingerstick ≥ 80 mg/L	**9.1**	0.2	41.3	**97.4**	96.7	97.9	**3.4**	0.5	22.5	**0.9**	0.8	1.1	**1.2**	0.0	6.5	**99.7**	99.4	99.8
	CRP value fingerstick ≥ 200 mg/L	**9.1**	0.2	41.3	**99.9**	99.7	100.0	**71.3**	8.6	588.0	**0.9**	0.8	1.1	**20.0**	0.5	71.6	**99.7**	99.4	99.8
specialist																			
	CRP value fingerstick ≥ 5 mg/L	**86.8**	82.2	90.6	**41.1**	39.8	42.5	**1.5**	1.4	1.6	**0.3**	0.2	0.4	**7.1**	6.3	8.0	**98.4**	97.7	98.8
	CRP value fingerstick ≥ 20 mg/L	**69.9**	64.0	75.2	**68.1**	66.8	69.3	**2.2**	2.0	2.4	**0.4**	0.4	0.5	**10.2**	8.9	11.7	**97.8**	97.2	98.2
	CRP value fingerstick ≥ 80 mg/L	**33.5**	27.9	39.4	**95.4**	94.8	95.9	**7.3**	5.9	8.9	**0.7**	0.6	0.8	**27.3**	22.6	32.5	**96.5**	96.0	97.0
	CRP value fingerstick ≥ 200 mg/L	**9.2**	6.0	13.3	**99.8**	99.6	99.9	**40.2**	20.4	79.1	**0.9**	0.9	0.9	**67.6**	50.2	82.0	**95.5**	94.9	96.0

GP: general practice; specialist: paediatric outpatient clinic and emergency department combined; LR+: positive likelihood ratio; LR-: negative likelihood ratio; PPV: positive predictive value; NPV: negative predictive value; 95% CI: 95% confidence intervals



Appendix 5.2: Scatter plot of C-reactive protein test result (fingerstick) and duration of fever (days).
C-reactive protein (CRP) test results are depicted in mg/L. After day 5 a clear drop in the number of high CRP values can be observed, with only 1 outlier at day 8 above 100 mg/L.

GENERAL DISCUSSION

Missing a diagnosis of serious infection in acutely ill children troubles every physician. Ten years ago, little research was performed on the value of signs and symptoms in diagnosing serious infections in acutely ill children in primary care. Most research originated from emergency department settings,[1-4] often not applicable to general practice, with differences in prevalence and patient characteristics. Evidence has shown that setting influences the value of different diagnostic tests, potentially rendering them useless in primary care.[5]

The Belgian healthcare system allows for unlimited access to paediatric outpatient clinics and emergency departments, alongside general practice. This provides us with a unique opportunity to examine acutely ill children in different urgent-access settings. The distribution of first-contact consultations in acutely ill children are scattered across these three settings, limiting the applicability of clinical prediction rules, which were designed in a different specific healthcare system. A recent large survey in Flanders by one of the largest mutual health insurance companies even claimed that 89% of parents preferred to consult the paediatrician directly.[6] This figure however is probably out-dated, as availability of outpatient paediatric care and improved collaboration between primary care paediatricians and GPs now call for a more stepwise and collaborative approach of acutely ill children.

A prospective cohort study in 2006 including over 4000 children in primary care resulted in the development of a clinical decision tree based on signs and symptoms to diagnose serious infections in acutely ill children.[7]
In a new but similar paediatric population with nearly 9000 inclusions, we validated the existing clinical prediction rule, derived in primary care, rigorously applying the same criteria as the derivation study for inclusion, exclusion and outcome definition. Approximately 0.7% of all children within this age range and 1.5% of all children below 5 years of age in Flanders were recruited.[8]
We used a pragmatic approach to facilitate the uptake of a symptom-based decision tree in further impact analysis and implementation and added the results of a point-of-care (POC) C-reactive protein (CRP) test to improve the rule's diagnostic performance, resulting in a stable model. Although residual uncertainty was present based on the available confidence intervals, we do not believe that future research will be able to refute these findings.
This improved prediction rule can effectively rule out serious infection in primary care and reduce the number of children without a serious infection deemed at high risk based on symptoms alone by applying a low CRP threshold.

As long as appropriate safety netting is installed to cope with potentially avoidable referrals or additional testing, this decision tree with POC CRP is ready to be implemented in general practice.
A decreasing incidence of serious infections in acutely ill children in general practice (**section I**) and the increasing inability to collect such a large sample in a primary care setting might be considered as important hurdles to conduct similar research in the future.
Future research should focus on the implementation of validated clinical prediction rules (**section II**) and POC tests (**section III**) and evaluate their cost-effectiveness when integrated in routine clinical care.
As no clinical prediction rule is perfect at ruling in serious infections, research on the most effective content and methods of delivery of appropriate safety netting advice (**section IV**) in ambulatory care is essential.

I. Incidence of serious infection in acutely ill children

Serious infections in children are usually defined as sepsis (including bacteraemia), meningitis, pneumonia, complicated urinary tract infection, bacterial gastroenteritis with dehydration, osteomyelitis, and cellulitis.[9] In contrast, acutely illness is one of the most common presentations of children to ambulatory care.
Infections account for 40% of all new episodes in general practice and 29% of all consultations in all ages in the UK.[10]
The total incidence of acute illness in primary care in children between 0 and 14 years of age is approximately 1.1 acute infections per child per year in Flanders, with even higher numbers in children below 4 years of age.[11]
The incidence of serious infections has declined over the past decade,[12] due to vaccination strategies and improvements in neonatal care, amongst other reasons. The immunization against Neisseria meningitidis serogroup C (in 2001), Haemophilus influenzae (2002), and Streptococcus pneumoniae (2007) has played an important role in this decline in Belgium. Observing a similar prevalence of serious infections in general practice in our study (0.3%) with a 9-year time interval since the 4-step decision tree derivation study (0.4%) assumes this decline to be stable.
However the increase and selection of other bacterial serotypes due to vaccination strategies, e.g. serotypes not included in the 13-valent pneumococcal vaccine for pneumococcal disease or serotype B for meningococcal disease, is still concerning healthcare policy makers worldwide. The development of novel vaccines against serotype B might substantially change the epidemiology of meningococcal disease in the future.[13, 14]

In a recent study at a Belgian emergency department, we found an incidence of 11%, with most serious infections in children below 4 years of age,[15] comparable to data up to 2007 in a study from the Netherlands.[16] A lower prevalence was found in two recent prospective studies in similar settings in the UK and Australia, with numbers comparable to our results in the specialist settings.[17, 18] A different definition of the composite outcome of serious infections might explain this difference in prevalence, e.g. the inclusion of viral infection with hypoxia or dehydration requiring a hospital admission in one study.[15]

Serious infections in primary care are dominated by pneumonia, with urinary tract infections in second place, and very few cases of sepsis, meningitis, or osteomyelitis.[7, 10] This was also the case in our study; we even did not observe any sepsis or meningitis cases in the GP setting.
This evolution in diagnostic categories within the serious infections spectrum might influence the further development and validation of clinical prediction rules: we may need to focus on pneumonia and UTI cases as sepsis or meningitis become less and less prevalent or even non-existent in this setting, rendering research on these cases almost impossible.

Even in the specialist setting (paediatric outpatient clinic and emergency department), we found only 1 out of 17 cases of meningitis to be of bacterial origin (post-neonatal Group B Streptococcal infection) and only 1 case of meningococcal sepsis, limiting the validity of clinical prediction rules developed to identify meningitis or sepsis based on skin and other clinical features, derived in an era that was dominated by meningococcal disease.[19, 20] Furthermore, the difficulty to identify serious infections will most likely increase at a declining prevalence, especially in the early stage of the disease when signs and symptoms are unspecific, even for meningococcal disease.[21, 22] A shift to a larger proportion of viral causes amongst the few meningitis-cases with often an atypical presentation at first-contact might complicate things even further.[22]

Luckily, none of the recruited children died during our study period.
In the past century, child mortality has fallen to very low rates in all developed countries. However, rates between and within countries vary widely. In a survey of infection-related deaths of children aged 1 month to 14 years of age between 2003 and 2005 before widespread immunization against Streptococcus pneumoniae, 1368 infection-related deaths were documented in England and Wales, 20% of all deaths in this age range.[23]

Although declining in prevalence, meningococcal disease is still the most common fatal bacterial infection, accounting for 24% of all deaths due to infectious diseases in children aged 1 month to 14 years.

Although the incidence has dropped over the past decade as mentioned above, the overall incidence in Europe is still 7.37 cases per 100000 per year in children younger than 4 years.[24]

In 2012, 44 childhood deaths (0.004% of all children between 0 and 14 years) in Flanders were caused by a serious infection. Infectious diseases are responsible for 13.8% of all deaths in children under the age of 1 year, and for 4.6% of deaths in children aged 1 to 14 years in Flanders.[25]
Putting these numbers into a broader perspective of overall childhood mortality, allows healthcare policy to be adjusted on a larger scale. Considering the high health expenditures in Belgium, the high overall mortality (also including road traffic accidents) in infants and children aged 1 to 4 years [26] is troublesome and should trigger healthcare policy makers to invest in risk modifying strategies to prevent avoidable deaths in general in these children.
To identify the factors that can modify this risk, national child death reviews are the first step to bring a broad perspective to the understanding why and how children die.[27] Health-system factors (e.g. training of paediatric caregivers to meet the needs of a diverse paediatric population) and socio-economic factors (e.g. ethnic origin, income inequality, access to care) can be considered important starting points to influence the risk of future deaths.[28]

II. Development of clinical prediction rules

The term clinical prediction rules covers a wide spectrum, but is usually defined as a clinical tool that quantifies the contribution of history taking, physical examination and (technological) diagnostic tests to stratify patients according to the probability of having a target disorder. Although other terms, such as “clinical prediction tool” or “clinical decision rule” have been suggested, clinical prediction rule is the most widespread used expression.

There is a widely accepted methodology for the development of clinical prediction rules.[29-31] The derivation of a clinical prediction rule is the first of three steps required before it can be disseminated and used in practice. This is followed by internal and external validation before finally testing the impact of its use on clinical outcomes.

These steps require cumulative levels of evidence and the adoption of several types of study designs to answer the relevant research and clinical questions. The increasing number of clinical prediction rules reported in the literature have a tendency to focus on the derivation stage with only a minority progressing to validation and very few undergoing impact analysis.[32, 33]

In a recent developed international register of clinical prediction rules clinical prediction rules for use in primary care, 434 unique clinical prediction rules were identified of which only 54.8% had been validated and 2.8% had undergone formal impact analysis. Most of these rules were developed for cardiovascular disease, respiratory, and musculoskeletal conditions.[34]

Clinical prediction rules are commonly derived through development techniques available for multivariable algorithms.
A few scoring systems, however, have been derived from bivariable analysis, such as the Alvarado score for acute appendicitis and the modified Glasgow score for acute pancreatitis.[35] Others are based on expert opinion, such as the APGAR score,[36] which after 50 years still remains valid and firmly embedded in routine care.[37]
A multivariable approach therefore does not guarantee better performance in subsequent validation, but has the main advantage (in most methods) of taking into account interactions between clinical predictors, adjusting for over-fitting and running diagnostics on the final model to locate cases with excessive influence on the model, enhancing the robustness of the final model.

The methods used to derive a multivariable algorithm are diverse and all have their advantages and disadvantages.
In our analyses, we preferred to use classification and regression tree (CART) analysis, a decision tree building method, based on non-parametric tests. It uses the most discriminative test at every node and dichotomizes continuous variables. It allows for multiple cross-validation and defining the minimum size split, avoiding over-fitting of the final model. It deals with missing values in an intelligent way, through surrogate splits and allows users to attribute weights to misclassification of cases. It is however prone to variability in the resulting trees and usually a large sample size is required, as was the case in our study.[38]

Other methods were considered less appropriate for our analyses:

(1) Simple tree building, although able to account for interactions, requires a deliberate choice of variables and their thresholds, which is almost impossible in datasets with a large number of tests or tests with continuous outcomes.

(2) Multiple logistic regression is a reasonably fast technique, again allowing for interactions and easy handling of continuous variables, as well as predicting multiple outcome categories (polytomous logistic regression). The main issue is the exclusion of subjects with missing values, unless an imputation of missing values technique is used, such as multiple imputations (often used inappropriately when the assumption of "missing at random" is clearly violated).[39, 40]
In our analyses, multiple imputation was not feasible, because the assumption of "missing at random" was probably violated, i.e. clinicians tend to record abnormal findings more often than normal findings. As a result, logistic regression was deemed unsuitable for our analysis.

(3) Other methods, originating form machine-learning methods, such as neural networks, random forests and Bayesian networks can be quite powerful and precise in their predictions, but are not for inexperienced researchers and or often considered to create a "black box phenomenon", and also struggle with missing values. We tested a number of such strategies on the data by Van den Bruel et al.[7] None of them superseded the performance of the initial analysis, which was performed using CART.[41]

Very few clinical prediction rules have undergone extensive validation, limiting the ability of clinicians or guideline groups to truly evaluate their performance and balance benefits and harms.[42] Clinical prediction rules tend to perform worse when validated in a new setting.[43] Often clinical prediction rules are only internally validated through split-sample or cross-validation, simply assessing the precision of a clinical prediction rule within its derivation sample. Naturally, this leads to an optimistic estimate of performance.[44] Narrow validation with similar conditions as the derivation cohort and broad validation in multiple different settings or different populations are essential to prepare a rule for further dissemination.

In our study we have validated the existing clinical prediction rule in a new but similar population at multiple sites (**Chapter 3**: temporal and geographic validation) and examined the diagnostic value in an international network of urgent-access ambulatory care settings (**Chapter 1**: broad fully independent validation). **Chapter 5** describes updating of the clinical prediction rule with a new test, namely POC CRP testing.

Recently, a statement regarding the reporting of multivariable prediction models for individual prognosis or diagnosis (TRIPOD) has been developed to improve the transparency of the reporting of prediction model studies regardless of the study methods used.[45] It includes a checklist recommended to authors of such studies. We believe we have met these criteria throughout this thesis and fully support the dissemination of the TRIPOD statement.

The integration of a validated clinical prediction rule into routine clinical practice presents a number of challenges, including mode of delivery of the clinical prediction rule at the point-of-care and the applicability of a clinical prediction rule derived in one setting to a new setting.[46]

The components of the clinical prediction rule should be clinically sensible, comprehensive and appropriate for the purpose of the rule. Preparing the rule for impact analysis and implementation includes identifying potential barriers to the use of the clinical prediction rule. For instance, an Australian impact analysis study of the Ottawa ankle rule considered and addressed barriers at an organizational, individual and societal level before conducting their study.[47]

Another important consideration is determining how the clinical prediction rule will be integrated into the clinical workflow. This may be achieved in different ways, for instance, incorporation of the clinical prediction rule as part of a broader guideline implementation and embedding the clinical prediction rule into clinical software or a computerized clinical decision support system (CDSS), as these have shown to modify physicians' test ordering behaviour.[48, 49] The use of digital point-of-care tests for e.g. vital signs or biomarkers communicating with the electronic medical record might enhance the uptake of the clinical prediction rule.

In the next phase, we need to determine whether the clinical prediction rule is effective; does it improve the process of clinical care, patient outcomes and increase cost-effectiveness.[30] Other important considerations are patient satisfaction and quality of life measures. They often require a (clustered) randomized trial.
If the impact analysis study shows a clinical prediction rule to be effective then the focus shifts to the translation of the clinical prediction rule from a research setting into everyday clinical practice delivered by the wider community of clinicians.[50] Re-evaluation after widespread implementation, e.g. through continuous morbidity registration networks,[51] can contribute to the success of this process.

III. USE OF POINT-OF-CARE TESTING IN GENERAL PRACTICE

Point-of-care (POC) tests are used at or near the site of the patient. They usually do not require permanent dedicated space and are performed outside the clinical laboratory, although a few exceptions occur (e.g. blood gas analyser in intensive care units or B natriuretic peptide testing in the core lab).

General practitioners used to pride themselves for being the "low technology medicine", which embodied a human and cheap approach to medicine. However, even Hippocrates was an experienced uroscopist, examining urine in 400 BC (admittedly only as a prognostic indicator) and eventually Theophilus introduced a innovative doctrine to use uroscopy for diagnosis of illnesses in 700 AD.[52]
Dipstick urinalysis is still the most used point-of-care test available in primary care to support diagnosis for a wide range of conditions.

There have been some POC devices (ultrasound devices, quick blood counts) available for research purposes in the early '90s, which were abandoned because they were too expensive, too large, and usually a combination of the above.

At present, devices are considerably smaller, more affordable, but more importantly, due to increasing research performed on biomarkers in primary care, more relevant to support clinical decision making.

Likewise, the industry is not missing out, moving devices from the professional setting at the lab to more non-traditional scenes as the GP's office and even patient self-monitoring. There are still discrepancies between the devices developed by industry and the needs of healthcare professionals in the field, but improved communication and interactions between industry, academia, and end-users might narrow this gap.

The development of POC tests is driven by many factors, such as testing opportunities (e.g. International Normalize Ratio (INR) testing at home, blood gas or cardiac enzymes at emergency scenes, Malaria-testing in refugee camps) as well as counselling opportunities (e.g. INR testing at the GP's office, HIV testing in STD clinics).

POC testing takes up 31% of the global in-vitro diagnostics market, and from 2009 to 2016 the US POCT market is expected to show a compound annual growth of 9.2%.[53]

EU governments see decentralized testing as a way to control the cost of delivering healthcare to their aging populations. They have started placing greater emphasis on the prediction and prevention of disease through more proactive diagnostics. As a result an increase is expected in the number of POC testing conducted as well as the POC testing locations, which do not have a legal framework yet.[54]

A recent survey in 5 countries (Australia, Belgium, The Netherlands, UK, and USA) examined the current and future use of point-of-care tests by primary care doctors.[55] Although differences exist between countries, POC tests have not generally been adopted in primary care. Barriers in primary care clinicians' attitudes towards blood POC tests include concerns about accuracy, over-reliance on tests and limited usefulness. Facilitators include improved diagnostic certainty, targeting of treatment, communication and shared decisions.[56]
Exploring the needs of clinicians can also benefit successful development and implementation of new tests. Infections were mentioned as one of the top 5 conditions for which Belgian respondents would like a POC test.
Although 75% of Belgian GPs would like to use POC CRP, only 3% actually currently used it, probably due to overlap with the participating GPs in our validation and added value of CRP study, as compared to 48% of GPs in the Netherlands (overall 19% in all five countries).
A POC CRP test was desired by more than half of respondents across all countries.[55]

The desired POC tests as well as conditions that clinicians claim POC tests would help them diagnose, should be the focus of future research. The current evidence-base for test effectiveness in acutely ill children in primary care is very mixed, although new projects, such as the Horizon Scanning reports by the Monitoring and Diagnosis Workgroup in Oxford are trying to bridge that gap as well as other recent work.[57-60]

Based on our experience, we suggest that the perfect POC test should:
(1) measure (preferably) several relevant tests
(2) be portable (e.g. fit a doctor's bag: 6 x 4 x 2 inches)
(3) be easy to use (e.g. no or few wires)
(4) have strong batteries
(5) allow repetitive testing (e.g. for monitoring or re-assessment)
(6) have a high resolution screen
(7) provide fast results (ideally less than 2', maximum 5')
(8) be reliable and valid
(9) be non invasive (except for biomarkers using capillary blood)
(10) transfer data wirelessly e.g. to a handheld device and the electronic medical record of the physician or hospital

Several issues should be addressed before widespread use of POC testing in primary care can be advocated.

We should:
(1) examine the cost-effectiveness of a POC test in all applicable target conditions in terms of healthcare gain and expenditures.
(2) involve end-users and patients in the implementation and use of the point-of-care tests.
(3) anticipate the complexity of data management generated by the POC tests and maintain a clear oversight. This includes training of healthcare professionals (and patients) and regular competency assessment, appropriate quality control documentation, planned quality performance, scheduled reporting, standardized billing and reimbursement strategies, managing multiple testing platforms, and interlinking vendor specific versus vendor neutral data management systems (interfaces to laboratory and hospital information systems).
(4) ensure that multiple instruments and multiple cartridges perform adequately and produce reliable results.
(5) establish a framework for verification and monitoring of analytical performance, including quality control, calibration verification, analytical measurement range verification, and regular check method comparability.

To ensure optimal analytical performance and user-friendliness of the device, I have conducted a pilot study on the selected POC CRP test, as described in **Chapter 4**.

For internal quality control, control positives provided by the manufacturer were measured at regular intervals to confirm the efficacy and correct performance of the test according to the manufacturer's instructions during the added value of CRP study (**Chapter 5**). A Failure Modes and Effects Analysis (FMEA) was performed with promising results to assess ease-of-use and the risk of measurement failures, although with some recommendations concerning error feedback and quality control. Collaboration with a centralized clinical laboratory would be desirable to avoid such issues.

As this thesis is being written, I am already preparing a first meeting with interested stakeholders (clinical biologists, general practitioners, academics) to discuss the framework of potential future implementation strategies of point-of-care testing in primary care after thoroughly investigating cost-effectiveness and acceptability of the proposed tests by end-users and patients.

Although communication between general practice and other partners in the field of POC testing are not yet optimal, contacts with other specialties (clinical laboratory, specialists, healthcare policy makers) and industry are increasing. Other opportunities, such as the increase of miniaturization of POC tests, the experience and network for testing accuracy and added value of POC tests, as well as the commercial value of deploying POC testing in general practice, might influence future development and research in the field of point-of-care testing in primary care.

IV. SAFETY NETTING IN ACUTELY ILL CHILDREN

A single test will never reach perfect sensitivity and specificity in real life. Clinicians need to deal with an ever-present level of clinical uncertainty. To tackle this, physicians often put a safety net in place, informing parents when to re-contact and which alarm signs are relevant to monitor.

GPs have to deal with situations with a very low likelihood of an underlying serious disease on a daily basis. They often rely on their gut feeling and apply safety netting, however little is known about the optimal use of these strategies.[61] Neighbour first introduced the term safety netting, and considered it as one of the compounds of a good consultation. It is described as creating a contingency plan and implementing procedures to ensure that the plan works out and that the patient is safe in any (un)-foreseen eventualities.[62]
Safety netting appears to play an important role in repeated medical help seeking for children with fever. A telephone questionnaire revealed that parents who were not 'safety netted' by their doctor were more likely to seek further care.[63]

Almond et al. provided a more detailed explanation of the content of safety net advice in relation to illnesses in children seen in general practice. Consensus was reached among general practitioners and paediatric emergency department consultants on five statements based on a modified Delphi approach. It should include: the existence of uncertainty, what exactly to look out for, how exactly to seek further help and what to expect about time course. The authors found no consensus about how this advice should be provided (e.g. verbal, written or other formats).[64]

In our prospective study (**Chapter 3**) as part of the clustered randomized controlled trial by Lemiengre et al,[65] a parent leaflet was used, depicting which signs to look out for and when to contact their physician.

This evidence-based leaflet was in accordance and approved by the Flemish agency for the well being of young children and their families (Kind en Gezin). The leaflet was adjusted based on suggestions by parents of various education levels visiting a health care centre who were asked to read the leaflet at their GP's office. Analyses of these interventions are still on-going.

The NICE guideline on feverish children recommends GPs to use safety netting by means of a traffic light system, discussed in **Chapter 1** and **2**.[66] Though it appears to be an important tool for clinicians, only few studies examined the actual use of this safety netting advice.

A recent qualitative study by Jones et al. noticed a range of safety netting techniques with many inconsistencies, concerning their relative effectiveness on a variety of outcomes such as referrals, admission rates, re-attendance to health care and parental understanding, anxiety and satisfaction.[67] The participating clinicians were unaware of any existing guidelines; neither did they receive any specific training on the subject.

In another recent qualitative study, interviewing 37 GPs, we found that, although GPs are unfamiliar with the term safety netting, they frequently apply such advice applying gut feeling and intuition. What's more, they do not feel a need for guidelines or any other formal form of support.
The content of their advice remains the same when dealing with different types of patients, but they adjust the wording to patient's characteristics and the illness in question. Checking whether parents understood the given advice proved to be rather difficult.[68]
Safety netting offers a useful framework for the patient's parents and improves the doctor patient relationship. Furthermore, safety netting can avoid legal issues. It fulfils an educational role and probably aids in reducing overconsumption of investigations, doctor visits and antibiotics.

Whether it is verbal advice, patient leaflets, or new forms of communication through social media, it is certain that physicians need to adopt these instruments to deal with the ever-present clinical uncertainty.

Serious infections are rare. To avoid serious complications or death, early recognition is crucial. Our analyses have improved detection of serious infections in general practice, without increasing the number of avoidable referrals or additional testing. In specialist settings POC CRP can help triage children. Future research should focus on the implementation of this decision tree, as well as defining the content of the advice given to parents of acutely ill children.

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APPENDICES

Appendix I: thesis abstract.

Background: Acute infection is the most common presentation of children to ambulatory care. In contrast, serious infections are rare and often present at an early stage. To avoid complications or death, early recognition and adequate referral are essential. In a recent large study children were included prospectively to construct a symptom-based decision tree with a sensitivity and negative predictive value of nearly 100%. To reduce the number of false positives, point-of-care (POC) tests might be useful, providing an immediate result at the bedside. The most probable candidate is C-reactive protein. Every clinician should reassure anxious parents of children with self-limiting illnesses. The improvement of diagnostic algorithms, the addition of technological devices and the sensible use of safety netting procedures could improve prognosis of seriously ill children.

Methods: First, we externally validated clinical prediction rules, identified by a systematic review, in 7 urgent-access datasets, as well as comparing these results to recent findings in other studies. After zooming in on the diagnostic value of the clinical prediction rules based on vital signs with potential to differentiate serious infections from the majority of self-limiting illnesses in an inpatient paediatric setting in the UK, we focused our analyses on the temporal & geographic validation of the decision tree based on signs and symptoms in a new but similar population in Flanders. We examined the analytical accuracy and user-friendliness of a POC test after careful selection of a device that meets all our requirements. Finally we explored the added value of the selected POC CRP test in a prospective diagnostic accuracy study in three different ambulatory care settings: general practice, outpatient paediatric clinic, and the emergency department.

Results: In low to intermediate prevalence settings the 4-step decision tree and evidence-based guidelines had high sensitivity, providing promising rule-out value for serious infections in 7 datasets. The paediatrician's overall illness assessment was the most useful feature to rule in sepsis or meningitis in a study of hospitalized children. Temporal validation of the 4-step decision tree indicated that this practical tool for diagnostic triage of acutely ill children in primary care is valid and ready to be implemented in routine care, if appropriate safety netting or additional testing is applied. The selected POC CRP test was accurate in children and should be considered reliable and user-friendly. Adding point-of-care CRP test results to the 4-step decision tree helped identifying serious infections in the GP setting and can potentially reduce the number of investigations and admissions in children with non-serious infections. I propose a new decision tree to be used in specialist settings as a triage instrument to safely rule out serious infections.

Discussion: The incidence of serious infections has declined over the past few years, amongst other reasons, due to vaccination strategies and improvements in neonatal care. Before a clinical prediction rule can be implemented in routine care, it has to go through several stages of development and testing. A single test will never reach perfect sensitivity and specificity in real life. To tackle the ever-present clinical uncertainty, physicians often put a safety net in place, informing parents when to re-contact and which alarm signs are relevant to monitor. I put an emphasis on these issues and offer a perspective for future developments in the field of point-of-care testing in serious infections in paediatric primary care.

Appendix II: about the author.

Jan Verbakel was born on 3 July 1983. His initial APGAR score was checked by Prof Eggermont, a consultant paediatrician at UZLeuven. At age 4, he caught a Mycoplasma pneumoniae-infection, which was uncommon in those days and difficult to diagnose, requiring a specialist admission for 10 days.
He grew up in the healthy Heverlee-forest air and finished high school on the green fields of the Sint-Albertuscollege in Haasrode with the option Ancient Greek-Mathematics.

Jan Verbakel finished his medical training in 2008 at KU Leuven. He started his GP training in a GP cooperative near Leuven under supervision of Dr. Jo Lisaerde and Dr. Lucia De Smet over a period of 3 years, during which he was offered a position as a PhD student at the "Academisch Centrum voor Huisartsgeneeskunde", KU Leuven, under supervision of Prof. Frank Buntinx. He affiliated with his GP trainers in Kessel-Lo and was appointed as nursing home physician at "De Wingerd", a dementia care facility in 2008 in Leuven and has temporarily worked as a civilian doctor for the Belgian air force and a preventive health care physician at "Kind en Gezin". He was invited for a 12-month visiting research fellowship at the Department of Primary Care Health Sciences at the University of Oxford in 2014 to engage in several new research projects, besides finishing his PhD training.

EDUCATION AND QUALIFICATIONS

Period	2014 - 2015
Institute	Department of Primary Care Health Sciences, University of Oxford
Position	Visiting Research Fellow
Period	2009 - present
Institute	KU Leuven, Department of General Practice Doctoral training in Biomedical Sciences
Period	2014
Education	EFGCP Good Clinical Practice Training (with certificate) for experienced researchers, Leuven
Period	2012
Education	Logistic Regression, S. Lemeshow, Erasmus Summer School Programme, Rotterdam, the Netherlands
Period	2008 - 2011
Institute	KU Leuven, Faculty of Medicine
Degree	Post-initial Master Primary Health Care (magna cum laude)
Period	2009
Education	Medical Biostatistics. Prof. Dr. G. Verbeke (KU Leuven)
Period	2009
Education	Workshop Systematic Reviews of Diagnostic Test Accuracy, Dutch Cochrane Centre, Amsterdam, the Netherlands
Period	2001 – 2008
Institute	KU Leuven, Faculty of Medicine
Degree	Bachelor of Medicine (magna cum laude) Master of Medicine (cum laude)

EMPLOYMENT HISTORY

Period	2011 - present
Self-employed	GP cooperative: Practice Brugberg, Leuven, BE, associates: Dr. Jo Lisaerde, Dr. Lucia De Smet
Period	2008 - 2011
Employer	GP training KU Leuven, BE
Period	2009 - 2010
Employer	Defence, 1 Wing Antenna Beauvechain, BE: Civilian Doctor
Period	2008 - present
Employer	“De Wingerd” (Dementia Care Facility, Leuven, BE): Nursing Home physician

SCIENTIFIC ACTIVITIES

Grants (awarded)

1. FWO (Research Foundation - Flanders) Travel Grant for a long stay abroad ref. V413614N (€19800 + travel expenses) Oxford (UK) from August 1st, 2014 till July 31st, 2015.
2. RIZIV (National Institute for Health and Disability Insurance, Belgium) (€661403) note CGV 2012/135: "Optimizing diagnostics and antibiotic prescribing rate in acutely ill children in Primary Care."
3. FWO (Research Foundation - Flanders) Research project 2008 ref. G067509N (€74500): "Point-of-care testing in acutely ill children in Primary Care: Added value in diagnosing serious infections and antibiotics prescribing rate?
4. Flemish Government: Summer School Support 2012 (€500): Erasmus Summer School Programme, Rotterdam.

Grants (participated)

1. NIHR Programme Grants for Applied Research ref. RP-PG-0407-10347: Development and implementation of new diagnostic technologies in primary care.
2. HTA project n° 07/37/05: Systematic review and validation of clinical prediction rules for identifying children with serious infections in urgent-access care.

Reviewer

1. invited peer reviewer for BMJ, BMJ open, Family Practice, BMC Med Res Methodol, Eur J Gen Pract, World J Gastroenterol, Swiss Med Wkly, Agency for Healthcare Research and Quality.

Teaching

1. Verbakel JY. Diagnosing serious infection in acutely ill children in ambulatory care: a clinical decision tree & POC CRP. Evidence Live conference 2015, Oxford University, Oxford, UK
2. Verbakel JY. Clinical prediction rules and POC CRP in acutely ill children in ambulatory care: the ERNIE 2 trial experience. Evidence-Based Diagnosis & Screening module of the MSc in Evidence-Based Health Care 2015, Oxford University, Oxford, UK
3. Verbakel JY. Clinical prediction rules and POC CRP in acutely ill children in ambulatory care: the ERNIE 2 trial experience. Departmental Seminar 2014, Oxford University, Oxford, UK
4. Verbakel JY. POCT in general practice. National POCT Symposium 2014, Antwerp, BE
5. Verbakel JY. POCT in medical practice. IMEC Academy "Nanotechnology for Health" 2014, Leuven, BE
6. Verbakel JY. Deriving multi-variable clinical prediction rules: a literature-base how-to. Literature seminar Doctoral School 2014, Leuven, BE

7. Verbakel JY. Management of acutely ill children: a chain of care as strong as the weakest link. Postgraduate distance learning (Pentalfa) 2013, KU Leuven, BE
8. Verbakel JY, Aertgeerts B. Diagnosing Acute illness in children. 1st year of Post-Initial Master of Primary Care 2012 – present, KU Leuven, BE
9. Verbakel JY, Stevens R, Buntinx F. Multiple External Validation of Clinical Prediction Rules, Adjusting CPRs and Individual Patient Data meta-analysis: methodological challenges. Society for Academic Primary Care conference 2011, Bristol, UK
10. Buntinx F, Verbakel JY. Prediction rules: validation. Clinical prediction rules International Working Group meeting 2010, Oxford, UK
11. Verbakel JY, Lemiengre M, De Sutter A, Aertgeerts B, Buntinx F. Added Value of Point-of-Care CRP for diagnostic triage in acutely ill children in General Practice. European General Practice Research Network conference 2010, Plovdiv, Bulgaria

OTHER SKILLS

Languages
1. Dutch: Mother tongue
2. French: Fluent
3. English: Fluent,
   Degree (magna cum laude) in Medical English (ILT Leuven)

Computer
1. Highly proficient in all Microsoft Office Applications, Adobe Creative Suite, Stata, SPSS, R statistical software, and many other IT applications

Music
1. Higher Degree in Percussion instruments, Chamber Music and Saxophone

Miscellaneous
1. Degree in Spirometry, Electrocardiography and Radiation Protection
2. First Aid training & CPR (2001, KU Leuven, BE)
3. Final Degree of Youth Leader and Youth Supervisor
4. Member of the County Council of Youth Affairs (City of Leuven, BE) 2001 - 2005
5. Driver's license (since 2002)

Interests Actuality, travel, culture (music, multimedia), literature, running

PERSONAL LIFE

Marital status married in 2011

Children 1 son, born in 2012

Appendix III: list of publications.

A1 PAPERS (INTERNATIONAL PEER-REVIEWED JOURNALS)

a. A1 Papers (published):

1. Verbakel JY, Lemiengre MB, De Burghgraeve T, De Sutter A, Bullens DM, Aertgeerts B, and Buntinx F, on behalf of the ERNIE 2 collaboration. Diagnosing serious infections in acutely ill children in ambulatory care (ERNIE2 study protocol, Part A): diagnostic accuracy of a clinical decision tree and added value of a point-of-care C-reactive protein test and oxygen saturation. ***BMC Pediatrics* 2014;14:207**.
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b. A1 Papers (submitted):

1. Verbakel JY, Lemiengre MB, De Burghgraeve T, De Sutter A, Aertgeerts B, Bullens DMA, Shinkins B, Van den Bruel A, Buntinx F. Validating a decision tree for serious infection in acutely ill children in ambulatory care.
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5. Renier W, Hoogma-von Winckelmann K, Verbakel JY, Aertgeerts B, Buntinx F. Signs and symptoms in adult patients with acute dyspnoea: a systematic review and meta-analysis.

A3 PAPERS (NATIONAL PEER-REVIEWED JOURNALS)

a. A3 Papers (published):

1. Verbakel JY. Ambulante behandeling van pneumonie bij kinderen: 5 of 10 dagen antibiotica? ***Minerva*** **2015;14(2):26.**
2. Verbakel JY. Point-of-care inschatting van de prognose van musculoskeletale pijn bij ouderen. ***Minerva*** **2014;13(4):41.**
3. Hoogwijs I, Verbakel JY, Aertgeerts B, Bullens D, Buntinx F. Ernstige infecties op een pediatrische spoedafdeling. ***Tijdschr voor Geneeskunde*** **2014;70(7):362-368.**
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Appendix IV: samenvatting.

Acute infectie is één van de meest voorkomende ziektebeelden bij kinderen in de eerste lijn.
Daarentegen zijn ernstige infecties zeldzaam bij kinderen in de westerse wereld, maar geassocieerd met aanzienlijke morbiditeit en mortaliteit.
In Vlaanderen zijn infectieziekten verantwoordelijk voor 13.8% van alle overlijdens in kinderen onder 1 jaar, en 4.6% van alle kinderen tussen 1 en 14 jaar. Ernstige infecties bij kinderen worden meestal gedefinieerd als sepsis (inclusief bacteriëmie), meningitis, pneumonie, gecompliceerde urineweginfectie, bacteriële gastro-enteritis met dehydratatie, osteomyelitis en cellulitis.

Zaak is deze ernstige infecties te onderscheiden van de grote groep van zelflimiterende infecties bij kinderen. In de eerste lijn, zal minder dan 1% van de acuut zieke kinderen evalueren naar een ernstige infectie.
De incidentie van ernstige infecties bij kinderen is 5 tot 10 maal hoger op de pediatrische spoedafdeling.

In een recente studie werden meer dan 4000 kinderen prospectief gerekruteerd om een beslisboom te ontwikkelen op basis van tekens en symptomen. De beslisboom had een sensitiviteit en negatief voorspellende waarde van bijna 100%. Echter de kans van een ernstige infectie bij kinderen die positief testen was ongeveer 6%. In dit proefschrift hebben we deze beslisboom gevalideerd in een nieuwe populatie en de toegevoegde waarde van point-of-care (POC) testen onderzocht in de diagnose van ernstige infecties bij acuut zieke kinderen in de eerste lijn.

POC testen zijn laboratorium- en andere testen die men kan uitvoeren en analyseren nabij de patiënt. De arts heeft dadelijk resultaat en kan het beleid onmiddellijk aanpassen. Deze testen zijn vooral interessant wanneer een snelle beslissing nodig is, zoals bij een spoedgeval. Ze zijn minimaal invasief en dus relevant in de pediatrische eerstelijnszorg.

Een systematische review identificeerde de laboratoriumtesten die bruikbaar zijn bij ernstige infecties bij kinderen met koorts in de ambulante praktijk. C-reactief proteïne (CRP) werd weerhouden als één van de beste kandidaten.
De huisarts gebruikt vaak vangnet-advies om het ziekte-inzicht van de patiënt (en ouders) te toetsen en advies te geven over alarmsignalen en wanneer opnieuw contact op te nemen.
De verbetering van diagnostische algoritmen, de toevoeging van point-of-care testen en het correct gebruik van vangnet-advies kan de prognose van ernstig zieke kinderen verbeteren.

DOELSTELLINGEN

De onderzoeksvraag van dit proefschrift was:
"Naast het meten van de klinische tekens en symptomen, kan nieuwe of bestaande technologie de vroegtijdige herkenning van ernstige zieke kinderen in de eerste lijn verbeteren?"

In hoofdstuk 1 zijn we dieper ingegaan op de klinische beslisregels geïdentificeerd door een recente systematische review gebaseerd op vitale tekens en symptomen. We hebben deze proberen valideren in 7 datasets van acuut zieke kinderen en heb de resultaten vergeleken met recente bevindingen uit andere studies.
Hoofdstuk 2 zoomde in op de waarde van de klinische beslisregels bestaande uit vitale tekens om ernstige infecties te onderscheiden van niet-ernstige infecties in een pediatrische ziekenhuisafdeling in het Verenigd Koninkrijk.
Hoofdstuk 3 beschreef de resultaten van onze validatie van een beslisboom op basis van tekens en symptomen in een nieuwe, maar vergelijkbare populatie in Vlaanderen.
Hoofdstuk 4, in voorbereiding van de grote prospectieve studie, betrof een haalbaarheidsstudie over het gebruik van de gekozen POC test in de pediatrische zorg. We bestudeerden de analytische nauwkeurigheid en gebruiksvriendelijkheid van een geselecteerde POC test na zorgvuldige selectie van een POC test die voldeed aan al onze voorwaarden.
Hoofdstuk 5 beschreef de resultaten van de prospectieve diagnostische accuraatheidsstudie, met tot doel de toegevoegde waarde van de POC CRP test in de eerstelijnsgezondheidszorg te verkennen. We richtten ons op de klinische bruikbaarheid van deze POC test in drie verschillende settings: de huisartspraktijk, de poliklinische kinderartspraktijk en de spoedafdeling.

De incidentie van ernstige infecties is afgenomen in de afgelopen jaren, onder andere als gevolg van vaccinatiecampagnes en verbeteringen in de neonatale zorg.
Alvorens een klinische beslisregel te implementeren in routinezorg, moet men verschillende stadia van ontwikkeling doorlopen.
Een enkele test kan nooit perfect gevoelig en specifiek zijn. Clinici moeten omgaan met een altijd aanwezige klinische onzekerheid. Artsen gebruiken vangnet-advies door ouders te informeren wanneer opnieuw contact te nemen en welke alarmtekens in het oog te houden.
De discussie beschreef deze vraagstukken, en trachtte een perspectief te bieden voor toekomstige ontwikkelingen op het gebied van POC testen in de diagnose van ernstige infecties bij kinderen in de eerste lijn.

KLINISCHE BESLISREGELS IN VERSCHILLENDE AMBULANTE SETTINGS

Beslisregels worden gepropageerd als hulpmiddel om herkenning van ernstige infecties te verbeteren. Een recente systematische review identificeerde zeven klinische beslisregels, waarvan er slechts één prospectief werd gevalideerd. Ons doel was de diagnostische waarde van deze regels in verschillende ambulante zorg populaties verspreid over West-Europa te onderzoeken.

Vier klinische beslisregels en twee nationale richtlijnen, op basis van klinische tekens en symptomen, werden retrospectief gevalideerd in zeven datasets, bestaande uit 11023 kinderen uit het Verenigd Koninkrijk, Nederland en België. In laag prevalente (LP) settings, hadden een 4-staps beslisboom en pneumonie-regel sensitiviteiten van >90% voor het uitsluiten van ernstige infecties. In intermediair prevalente (IP) settings, hadden de 4-staps beslisboom, pneumonie-regel, en Yale Observation Scale sensitiviteiten tussen de 22 en 88%. In een hoog prevalente (HP) setting, leverde de 4-staps beslisboom een sensitiviteit van 23%. In LP of IP-settings varieerde de sensitiviteit van de “National Institute for Clinical Excellence (NICE)”-richtlijn voor kinderen met koorts en de alarmtekens van het Nederlands Huisartsen Genootschap van 81 tot 100%.

Geen van de klinische beslisregels in deze studie leverde perfecte diagnostische nauwkeurigheid. In LP of IP-settings, had de 4-staps beslisboom en de evidence-based richtlijnen de hoogste sensitiviteit om ernstige infecties uit te sluiten, steeds met een bepaalde hoeveelheid onzekerheid. Geen van de beslisregels geïdentificeerd leek nuttig voor HP-settings, zoals spoedafdelingen.

KLINISCHE BESLISREGELS IN EEN PEDIATRISCHE ZIEKENHUISAFDELING

Kinderartsen worden dagelijks geconfronteerd met de uitdaging om de enkele kinderen met meningitis of sepsis te onderscheiden van de grote groep met zelflimiterende ziekte. Ons doel was de diagnostische waarde van de klinische kenmerken en hun beslisregels te onderzoeken om kinderen met sepsis of meningitis te identificeren bij acuut zieke kinderen opgenomen in een regionaal ziekenhuis in het Verenigd Koninkrijk.

Deze case-control studie liep tussen 2000 en 2005. We onderzochten de diagnostische accuraatheid van de individuele klinische tekens en 6 beslisregels, waaronder het NICE stoplicht-systeem, om de klinische bruikbaarheid te bepalen bij het identificeren van kinderen met een diagnose van sepsis of meningitis.

Verlies van bewustzijn, verlengde capillaire refill, verminderde alertheid, bemoeilijkt ademen, het oordeel van de arts dat het kind ernstig ziek was, hadden hoge positieve likelihood ratio’s (9-114) met brede betrouwbaarheidsintervallen, om sepsis of meningitis aan te tonen.

Het NICE stoplicht-systeem, de gewijzigde Yale Observation Scale, en de Paediatric Advance Warning Score deden het slecht met positieve likelihood ratio's, variërend van 1 tot 3.
De beoordeling van de algemene ziekte-indruk door de kinderarts bleek de beste voorspeller van sepsis of meningitis bij deze gehospitaliseerde kinderen. Klinische beslisregels konden sepsis of meningitis niet effectief aantonen. Enkele klinische symptomen kunnen deze scores aanvullen om sepsis of meningitis aan te tonen. Verder onderzoek is nodig om deze beslisregels te valideren.

VALIDATIE VAN DE 4-STAPS BESLISBOOM

We valideerden de 4-staps beslisboom in een prospectieve diagnostische accuraatheidsstudie. Acuut zieke kinderen die zich aanmeldden bij een huisarts of kinderarts werden consecutief gerekruteerd in Vlaanderen. Artsen werd gevraagd de 4-staps beslisboom te scoren, naast een grondige klinische evaluatie en gebruikelijke zorg. De bestudeerde uitkomst was ziekenhuisopname meer dan 24 uur met een ernstige infectie binnen 5 dagen na eerste contact. We rapporteerden de diagnostische accuraatheid van de beslisboom in sensitiviteit, specificiteit en positief en negatief voorspellende waarden.
We vonden een sensitiviteit en negatief voorspellende waarde van 100% in de huisartsensetting, perfect dus om ernstige infecties uit te sluiten.
Dit praktisch hulpmiddel voor diagnostische triage van acuut zieke kinderen in de eerste lijn bleek valabel en is klaar voor implementatie in routinezorg, op voorwaarde dat vangnet-advies en bijkomende testen worden aangewend.

ANALYTISCHE ACCURAATHEID VAN EEN POC CRP TEST

CRP is een acute-fase eiwit, gesynthetiseerd in reactie op een infectie of ontsteking. Veneuze bloedafname is niet evident bij kinderen in de ambulante praktijk. Een POC test op een druppel bloed geef dadelijk resultaat en is vooral nuttig bij kinderen.
Vorige generaties van POC CRP testen bleken goede correlatie met standaard laboratoriumtesten te hebben in studies in de eerste lijn en spoedgevallen. Het meten van CRP zou kunnen bijdragen aan de klinische besluitvorming in de diagnose van een ernstige infectie.
We konden de analytische accuraatheid van de Afinion POC CRP-test bevestigen in vergelijking met een immunoturbidimetrische CRP-test op een Cobas c702 toestel, zowel bij kinderen als volwassenen. Zelfs bij hoge CRP-concentraties, bleek de test nauwkeurig. De weinige verschillen tussen beide methoden bij lage CRP niveaus bleken klinisch niet significant. Alle deelnemende artsen en de hoofdonderzoekers achtten de test gebruiksvriendelijk.

TOEGEVOEGDE WAARDE VAN EEN POC CRP TEST IN DE AMBULANTE PRAKTIJK

Om het aantal vals-positieve testresultaten op de gevalideerde 4-staps beslisboom in de eerste lijn te verminderen, zou de POC CRP-test een belangrijke rol kunnen spelen.

In de diagnostische accuraatheidsstudie, hierboven vermeld, kregen kinderen die positief testten op de beslisboom een POC CRP-test. We rapporteerden de diagnostische accuraatheid van de beslisboom in combinatie met de POC CRP-testresultaten in sensitiviteit, specificiteit, positieve en negatieve likelihood ratio's en positieve en negatieve voorspellende waarden.

Het toevoegen van de resultaten van het POC CRP-test aan de beslisboom verhoogde de specificiteit naar 89.5% (95% CI 88.3-90.5%), met een sensitiviteit van 100% (95% CI 71.5-100%) in de huisartsensetting. Een nieuw ontwikkelde beslisboom gebaseerd op eenvoudig-te-beoordelen klinische tekens werd ontwikkeld in de ziekenhuissetting, met een sensitiviteit van 97.1% (95% CI 94.3-98.7%) en een negatief voorspellende waarde van 99.6% (95% CI 99.2-99.8%).

Het toevoegen van POC CRP-testresultaten aan een gevalideerde beslisboom hielp ernstige infecties te identificeren in de huisartsensetting en kan het aantal onderzoeken en opnames bij kinderen met niet-ernstige infecties mogelijk verminderen. Dit model is klaar voor implementatie in de huisartspraktijk. We stellen een nieuwe beslisboom voor als triage instrument om ernstige infecties uit te sluiten in de ziekenhuis setting.

DISCUSSIE

We hebben een bestaande klinische beslisregel, afgeleid in de eerste lijn, gevalideerd in een nieuwe maar vergelijkbare populatie van bijna 9000 inclusies bij acuut zieke kinderen. We gebruikten een pragmatische aanpak om de disseminatie van de klinische beslisregel in de dagelijkse praktijk te vergemakkelijken en voegden de resultaten van een POC CRP test toe om de diagnostische waarde van de regel te verbeteren. Dit leidde tot een stabiel model effectief in het uitsluiten van ernstige infecties in de eerste lijn met het potentieel om het aantal vermijdbare verwijzingen en onderzoeken te reduceren.

Toekomstig onderzoek moet zich richten op de implementatie van gevalideerde klinische beslisregels en POC testen en hun kosten-baten evalueren. Aangezien geen enkele klinische beslisregel perfect is om ernstige infecties aan te tonen, is er onderzoek nodig naar de meest effectieve inhoud en toepassing van vangnet-advies in de ambulante praktijk.

Appendix V: summary.

Acute infection is one of the most common problems of children attending primary care. In contrast, serious infections are rare in children in developed countries, but associated with considerable morbidity and mortality. In Flanders, infectious diseases are responsible for 13.8% of all deaths in children under the age of one year, and for 4.6% of deaths in children aged 1 to 14 years. Serious infections in children are usually defined as sepsis (including bacteraemia), meningitis, pneumonia, complicated urinary tract infection, bacterial gastroenteritis with dehydration, osteomyelitis, and cellulitis.

These serious infections need to be distinguished from the vast majority of self-limiting infections in children. In a primary care setting, less than 1% of children assessed will have a serious infection. The incidence of serious infections in children is assumed to be 5 to 10 times higher at the paediatric emergency department, as seen in one of our recent studies.

In a recent study, over 4000 children were included prospectively to construct a decision tree based on signs and symptoms. The decision tree had a sensitivity and negative predictive value of nearly 100%. The probability, however, of having a serious infection in children testing positive, was approximately 6%. In this thesis, I aimed to validate this decision tree in a new population and explore the added value of technological tests, such as point-of-care (POC) tests in diagnosing serious infection in acutely ill children in primary care.

POC tests are defined as laboratory and other services provided to patients at the bedside. The physician has an immediate result and management can be adjusted accordingly. This makes them especially attractive in situations where a fast decision is warranted, such as urgent-access primary care. They are minimally invasive, and thus relevant in paediatric care.
A systematic review identified the laboratory tests used to detect serious infections in febrile children in ambulatory settings. C-reactive protein (CRP) is one of the most probable candidates for this purpose.

The general practitioner often puts a safety net procedure in place in order to clarify the patient's knowledge of the current illness and to advice on alarming signs and when to re-consult in specific situations. The improvement of diagnostic algorithms, the addition of technological tests and the sensible use of safety netting procedures could improve prognosis of seriously ill children.

OBJECTIVES

Vital signs and clinical features can play an important role in confirming or excluding the possibility of serious infection in children presenting to an ambulatory care setting. Van den Bruel et al. demonstrated that a decision tree based on signs and symptoms could be constructed with a negative predictive value of nearly 100%. If applied in clinical practice without caution, this decision tree could cause far too many children to be referred to specialist.

The research question of this thesis was:
"In addition to measuring clinical signs and symptoms, can new or existing technology improve the early identification of seriously ill children in primary care?"

In chapter 1 we focused on the clinical prediction rules identified by a recent systematic review based on vital signs and symptoms only and try to validate these rules in an 7 urgent-access datasets, as well as comparing these results to recent findings in other studies.
Chapter 2 zoomed in on the value of the clinical prediction rules based on vital signs with potential to differentiate serious infections from the majority of self-limiting illnesses in an inpatient paediatric setting in the UK.
Chapter 3 described the results of a temporal & geographic validation of the decision tree based on signs and symptoms in a new but similar population in Flanders.
Chapter 4 set the scene for a large prospective trial with a feasibility study on the use of the POC test in the intended setting, namely ambulatory primary care. We examined the analytical accuracy and user-friendliness of a selected POC test after careful selection of a device that meets all our preliminary requirements.
Chapter 5 described the results of the prospective diagnostic accuracy study, aiming to explore the added value of selected POC tests in primary care. We focused on the clinical utility of these POC tests in three different ambulatory care settings: general practice, outpatient paediatric clinic, and the emergency department.
The incidence of serious infections has declined over the past few years, amongst other reasons, due to vaccination strategies and improvements in neonatal care.
Before a clinical prediction rule can be implemented in routine care, it has to go through several stages of development and testing.
A single test will never reach perfect sensitivity and specificity in real life. Clinicians need to deal with an ever-present level of clinical uncertainty. To tackle this, physicians often put a safety net in place, informing parents when to re-contact and which alarm signs are relevant to monitor.

The final discussion put an emphasis on these issues and offered a perspective for future developments in the field of POC testing in serious infections in paediatric primary care.

CLINICAL PREDICTION RULES IN DIFFERENT AMBULATORY CARE SETTINGS

Prediction rules are promoted as a means to improve recognition of serious infections. A recent systematic review identified seven clinical prediction rules, of which only one had been prospectively validated, calling into question their appropriateness for clinical practice. We aimed to examine the diagnostic accuracy of these rules in different ambulatory care populations in Europe.

Four clinical prediction rules and two national guidelines, based on signs and symptoms, were validated retrospectively in seven individual patient datasets from primary care and emergency departments, comprising 11,023 children from the UK, the Netherlands, and Belgium. In low prevalence (LP) settings, a 4-step decision tree and a pneumonia rule had sensitivities of >90% (at a negative likelihood ratio (NLR) of < 0.2) for ruling out serious infections. In intermediate prevalence (IP) settings, the 4-step decision tree, the pneumonia rule, and YOS had sensitivities between 22 and 88%, with NLR ranging from 0.3 to 0.8. In a high prevalence (HP) setting, the 4-step decision tree provided a sensitivity of 23%. In LP or IP settings, the sensitivities of the National Institute for Clinical Excellence guideline for feverish illness and the Dutch College of General Practitioners alarm symptoms ranged from 81 to 100%.

None of the clinical prediction rules examined in this study provided perfect diagnostic accuracy. In LP or IP settings, the 4-step decision tree and evidence-based guidelines had high sensitivity, providing promising rule-out value for serious infections in these datasets, although all had a percentage of residual uncertainty. None of the prediction rules identified seemed to be valuable for HP settings such as emergency departments.

CLINICAL PREDICTION RULES IN INPATIENT PAEDIATRIC SETTING

Clinical staff at acute paediatric services faces the challenge of differentiating the few children with meningitis or sepsis from the majority with self-limiting illness. We aimed to determine the diagnostic value of clinical features and their prediction rules for identifying children with sepsis or meningitis among those children admitted to a District General Specialist (DGH) with acute febrile illness.

Acutely ill children admitted to a DGH in England were included in this case-control study between 2000 and 2005. We examined the diagnostic accuracy of individual clinical signs and 6 clinical prediction rules, including the National Institute for Clinical Excellence ‘‘traffic light’’ system, to determine clinical utility in identifying children with a diagnosis of sepsis or meningitis.

Loss of consciousness, prolonged capillary refill, decreased alert- ness, respiratory effort, and the physician's illness assessment had high positive likelihood ratios (9-114), although with wide confidence intervals, to rule in sepsis or meningitis. The National Institute for Clinical Excellence traffic light system, the modified Yale Observation Scale, and the Paediatric Advanced Warning Score performed poorly with positive likelihood ratios ranging from 1 to 3.
The paediatrician's overall illness assessment was the most useful feature to rule in sepsis or meningitis in these hospitalized children. Clinical prediction rules did not effectively rule in sepsis or meningitis. The modified Yale Observation Scale should be used with caution. Single clinical signs could complement these scores to rule in sepsis or meningitis. Further research is needed to validate these clinical prediction rules.

TEMPORAL & GEOGRAPHIC VALIDATION OF THE 4-STEP DECISION TREE

In a prospective diagnostic accuracy study we validated the 4-step decision tree for serious infections. Acutely ill children presenting to a general practitioner or paediatrician were included consecutively in Flanders, Belgium. Physicians were asked to score the 4-step decision tree, in addition to a thorough clinical assessment and their usual care. The outcome of interest was specialist admission more than 24 hours with a serious infection within 5 days. We reported the diagnostic accuracy of the decision tree in sensitivity, specificity, and positive and negative predictive values.
Reaching both sensitivity and negative predictive value of 100% in the GP setting, the 4-step decision tree performed as intended, to rule out serious infections.
This practical tool for diagnostic triage of acutely ill children in primary care has shown to be valid and is ready to be implemented in routine care, if appropriate safety netting or additional testing is applied.

ANALYTICAL ACCURACY OF A POC CRP TEST

CRP is an acute-phase protein, secreted in response to any infection or inflammation. Venous blood sampling can be difficult in children in ambulatory care. A POC test, provided at the bedside, presents an immediate result from a droplet of blood and is especially useful in children.
Previous generations of POC CRP tests have shown good correlation with standard laboratory tests in studies in primary care and emergency departments. Measuring CRP could contribute to clinical decision-making in diagnosing serious infection.

We were able to confirm the analytical accuracy of the Afinion POC CRP test in comparison with an immunoturbidimetric CRP test on a Cobas c702 device in children as well as in adults. Even at high CRP concentrations, the test demonstrated high agreement and precise measurements. The few differences between both methods in cases with low CRP levels were not found to be clinically significant, as they would not change decisions on further treatment or testing.
All participating physicians and the principal investigators deemed the device user-friendly.

ADDED VALUE OF A POC CRP TEST IN AMBULATORY CARE

To reduce the number of false positive test results on the validated 4-step decision tree in primary care, the POC CRP test might be useful, providing an immediate result at the bedside.

In the diagnostic accuracy study, mentioned above, children testing positive on the decision tree got a POC CRP test. We reported the diagnostic accuracy of the decision tree in combination with the POC CRP test result in sensitivity, specificity, positive and negative likelihood ratios and positive and negative predictive values.

Adding the results of the POC CRP test to the decision tree increased the specificity to 89.5% (95%CI 88.3 - 90.5%) while maintaining a sensitivity of 100% (95% CI 71.5 - 100%) in the GP setting. A newly developed decision tree, based on objective easy-to-assess clinical features was developed in the specialist setting, reaching a sensitivity of 97.1% (95% CI 94.3-98.7%) and a negative predictive value of 99.6% (95% CI 99.2-99.8%).

Adding POC CRP test results to a validated signs and symptoms-based decision tree helped identifying serious infections in the GP setting and can potentially reduce the number of investigations and admissions in children with non-serious infections. This model is ready for impact analysis and implementation in general practice. We propose a new decision tree to be used in specialist settings as a triage instrument to safely rule out serious infections.

DISCUSSION

The Belgian healthcare system allows for unlimited access to paediatric outpatient clinics and emergency departments, alongside general practice.

We have validated an existing clinical prediction rule, derived in primary care, in a new but similar paediatric population of nearly 9000 inclusions, rigorously applying the same criteria as the derivation study for inclusion, exclusion and outcome definition. We recruited approximately 0.7% of all children within this age range in Flanders and 1.5% of all children below 5 years of age.

We have used a pragmatic approach to facilitate the uptake of the clinical prediction rule in routine care and added the results of a POC test to improve the rule's diagnostic performance, resulting in a stable model effective at ruling out serious infections in primary care, leaving a certain amount of potentially avoidable referrals or additional testing, where safety netting plays an important role. Although residual uncertainty was present based on the available confidence intervals, we do not believe that future research will be able to refute these findings.

A decreasing incidence of serious infections in acutely ill children in general practice and the inability to collect such a large sample in a primary care setting might be considered as important hurdles to conduct similar research.

Future research should focus on the implementation of validated clinical prediction rules and POC tests and evaluate their cost-effectiveness when integrated in routine clinical care.

As no clinical prediction rule is perfect at ruling in serious infections, research on the most effective content and methods of delivery of appropriate safety netting advice in ambulatory care is essential.

Appendix VI: thanks to …

Silent gratitude isn't much use to anyone - G.B. Stern

Writing up this thesis, I realised I have a lot to be thankful for.
Above all for the people who surround me and support me.

Frank, u heeft mij deze kans geboden en ik ben u enorm dankbaar om vanaf dag een in mij te geloven. Uw betrokkenheid is zeldzaam bij een promotor en uw kalmte heeft mij altijd weten geruststellen. Ik vergeet vaak context te geven bij een onderwerp, maar iedereen die Frank kent, weet dat dit niet nodig is, gezien u binnen 5 minuten de pijnpunten weet bloot te leggen. Ik ga ervan uit dat ik niet uw laatste doctoraatsstudent zal zijn en hoop nog veel met u te mogen samenwerken.

Bert, als mijn adoptie-co-promotor, heeft u mij vanaf het begin geleerd in klare taal te spreken en niet te gaan zweven. Ik ben dankbaar voor uw oprechtheid en uw relativeringszin en ben trots met u als hoofd aan onze afdeling huisartsgeneeskunde.

An, als copromotor vanuit UGent wist u altijd probleemloos de afstand te overbruggen, zij het fysiek dan wel via Skype. Uw aanmoedigende woorden hebben mij doorheen dit project tot in de laatste fase steeds weten motiveren om de lat hoger te leggen.

Ann, een parabool snijdt een rechte in twee punten en ook zo was jij bij het begin en het einde van dit project betrokken. Het was even slikken toen jij naar Oxford trok, maar gezien mijn huidige affiliatie kan ik moeilijk zeggen dat ik daar spijt van heb. Ik wil u danken om nooit half werk te doen bij het becommentariëren van mijn teksten en het vertrouwen. Je kan op mijn enthousiasme rekenen voor verdere samenwerking.

Marieke, toen we in 2009 voor de eerste keer samenzaten in Gent, droomden we beiden van een grote dataset van zieke kinderen. We hebben de nodige tegenslagen gehad bij de zoektocht naar financiering, maar dankzij onze gebundelde krachten zijn we er toch geraakt. Uw twee flinke zonen en onze Jonas kunnen getuigen dat we hard gewerkt hebben met toch de nodige balans tussen werk en privé.

Tine, je hebt dit project ter harte genomen en mij in elke fase bijgestaan, van de torens registratieformulieren tot de jobstudenten-sweatshop tijdens de database-invoer. Zoals Bert zo eloquent bevroeg tijdens uw sollicitatie "Waarom komt een postdoc onderzoeker werken voor een snotneus zoals Jan?" Was het misschien onze bureau op de belle-vue van de afdeling of de ERNIE2-taarten met mascarponevulling? Ik denk dat het de werkethos en visie waren die we delen.

Rafael, you made me feel welcome at the Department of Primary Care Health Sciences in Oxford. You are an inspiration for every clinician interested in biostatistics and have such a naturel when discussing clinical subjects; one would almost assume you are a general practitioner, disguised as a statistician.

Thank you for your support and your willingness to travel to my hometown to jury my thesis.

Professor Hobbs, dear Richard, thank you for hosting my visiting research fellowship in Oxford and I hope to continue our collaboration in the future.

Matthew, I am grateful for your help and input throughout my PhD project. Your standing invitations to work with you in Oxford were greatly appreciated and kept me motivated while resulting in several collaborative publications.

David, much obliged for your guidance and input from day 1 and in preparing this presentation.

Richard, thank you for teaching me to think like a (bio)-statistician, always making sure the statistics are appropriate for the purpose of the analysis.

Dear Beth, thank you for listening and helping me out at a crucial point in my analysis. Your input is greatly appreciated.

Monica, it was an honour to work with you and I would very much like to continue our fruitful collaboration to further bridge the gap between GP- and hospital-based research.
I would like to thank the other members of the European Network for Recognising Serious Infections (ERNIE) for their views and support.

Roddy, thank you for your impressive work ethic collecting data on acutely ill children at Pinderfields hospital, registering all clinically relevant predictors.

Sta me toe de andere leden van de jury te bedanken: Isabelle, dank voor uw begeleiding en om samen de MCH bijscholing te verzorgen, Lars, dank voor uw rondleiding op de pediatrisch intensieve zorgen, de enige manier om voeling te krijgen met ernstig zieke kinderen, Jean-Bernard, u heeft steeds tijd gemaakt voor mij; uw visie op urgentiegeneeskunde is inspirerend, Andre, dank voor uw input halverwege mijn PhD project in aansluiting op uw lezing in Leuven.

Dominique, bedankt voor uw kritische blik vanaf dag 1 en uw hulp bij de zoektocht naar partners in de kindergeneeskunde in heel Vlaanderen. Chris, als diensthoofd heeft u steeds deze studie gesteund waarvoor ik u dankbaar ben.

Marc en Luc, dank om uw collega's te overtuigen en bij te dragen aan de datacollectie. Marie-Paule, Heidi, Alex, uw bijdrage aan de studie was van vitaal belang.
Dank ook aan Frederick (voor de omwegen door het Vlaamse land), Greet en Annelien die Oost- en West-Vlaanderen doorkruisten voor de studie.

Peter, sinds ons eerste telefoontje ontbrak het u, evenals de mensen van Alere, niet aan visie, waarvoor dank.

Beste Mr. Thijs, beste Fons, ik wil u danken voor de selectie van dit project uit velen en de ondersteuning vanuit het RIZIV. Uw visie heeft geholpen dit project waar te maken, waarvoor we Dr. Ri De Ridder eveneens dankbaar zijn.

Marina, dank voor uw steun doorheen dit project. Zonder u zou er zoveel meer mislopen dan we zelf durven toegeven. Dank ook aan Katrien voor het talloze rekenwerk en leuke babbels, Martine, Monique, Elizabeth voor uw steun op alle vlak.

Alle collega's van het ACHG die me deze kans geboden hebben, wens ik bijzonder te bedanken.

Mijn collega's op de praktijk, in het bijzonder Jo en Lucia, dank voor het vertrouwen en de bereidheid mij als halftijds HAIO aan te werven en mij te verwelkomen in de associatie. Ook mijn patiënten ben ik dankbaar voor het begrip tijdens mijn afwezigheid.

Aan alle vrienden die voor de welkome afleidingen zorgden: niets zo ontspannend als een Ardennen-weekend met blauwe jello of een tuinfeest met plons in de moerasvijver om alles te relativeren: Gust, Michiel, Arnout, Pieterjan, Vincent, Marin, Serge, Tom, Kris, Julie, Anneke, Marjan, Lore, Lore, Annelies, Isabelle, An, Lien, Bart, Hendrik, Lieven: merci!
Ook de jaargenoten voor hun oprechte interesse in mijn onderzoek en de winter-barbecues in Saint-Hubert: Evelien, Evelien, Alix, Lien, Katleen, Jasmien, Inneke, Christine, Lotte, Laura, Julie, Anne-Sophie, Klaar, en hun partners, en vooral aan Pol en Maarten om toch wat mannelijk tegengewicht te bieden in ons jaar.

Lieve ouders, ik ben jullie dankbaar om ons op te voeden met een gezonde nieuwsgierigheid voor wetenschap en ons aan te moedigen om ons best te doen in wat we ook doen. Maar ik ben eigenlijk vooral dankbaar en trots op wie jullie zijn: hartelijk, liefdevol en fantastische (groot)ouders voor ons gezin.

Ward, uw substantiële inbreng aan de cover en uitnodiging is niet te onderschatten, maar vooral bedankt voor uw ongezouten mening en eerlijkheid. Als recordhouder bezoekjes-in-London slaag je erin onze Jonas te verwennen en ons huis weg van huis te weren van heimwee.

Els, of Elsje zoals Jonas zegt, jij weet maar al te goed wat een thesis met zich meebrengt en deze kan nu met een grote rode strik naast die van u in ons familiearchief. Bedankt voor uw energie om de afstand die vaak groot lijkt te overbruggen, met bezoekjes, Skype-sessies en uw twee schatten van kinderen.

Dominique, mijn vrouw, dank u voor uw ongelooflijke geduld, zowel met mij tijdens dit project als met onze lieve zoon. Ik heb u beloofd deel 2 en 3 van onze trilogie samen te beleven. Nu sluit dit boekje: beschouw het als een proloog op deel 2 van ons leven.
Jonas, het zonnetje in mijn leven, papa is nu klaar met zijn boekje, nu kunnen we weer verder lezen in jouw favoriete boekje "we're going on a bear hunt". Lieve schatten, ik hou van jullie!

Deze thesis werd financieel ondersteund door het Rijksinstituut voor Ziekte- en Invaliditeitsverzekering (RIZIV, BE) onder referentie CGV 2012/235, het FWO onder referentie G067509N, het Health Technology Assessment Programme (HTA, UK) onder projectreferentie 07/37/05 en de National Institute for Health Research (NIHR, UK) onder referentie RP-PG-0407-10347. De meningen in deze publicatie zijn deze van de auteurs en niet noodzakelijk van de NHS, NIHR, FWO of RIZIV.

Dank aan Mevr. Sabrina Requejo van IKEA Belgium voor de vingerpopjes tijdens onze veldstudie.

Ik wil graag alle artsen bedanken voor hun deelname aan dit project en het includeren van acuut zieke kinderen:
dr. Aagje Pareyn, dr. Agnes Coenegrachts, dr. Agnes Liebert, dr. Alain De Mûelenaere, dr. Alexander Baekelandt, dr. Alja Lammens, dr. An Ramon, dr. An Weerts, dr. An-Sophie Vandenbulcke, dr. Anaïs Vandendriessche, dr. Ann Heyneman, dr. Ann Mandervelt, dr. Anne Desot, dr. Anneleen Cloots, dr. Anneleen De Bonte, dr. Anneleen Notebaert, dr. Annelies Raes, dr. Annelies Van Raemdonck, dr. Annemie Janssens, dr. Annemie Wijnants, dr. Areski Boumendil, dr. Barbara De Wilde, dr. Bea Vanheule, dr. Ben Hören, dr. Benedicte Lambrechts, dr. Berthold Aman, dr. Carolin Van Rossem, dr. Caroline Buyck, dr. Caroline Elsing, dr. Caroline Vanwelden, dr. Christine Balcaen, dr. Claudia Golen, dr. Daan Witdouck, dr. Daisy Rymen, dr. Danielle Van Bruggen, dr. Deepanjali Custers, dr. Delphine Magniette, dr. Didier Baert, dr. Diederik Van Sassenbroeck, dr. Diëgo Schrans, dr. Dirk Anseeuw, dr. Dirk Hofkens, dr. Dirk Peeters, dr. Dirk Vermandere, dr. Eddy Van Hollebeke, dr. Elisabeth Rundfeldt, dr. Elke Janssens, dr. Elke Van Hoyweghen, dr. Ellen De Ceunynck, dr. Els Deroose, dr. Els Ide, dr. Els Pieters, dr. Emilie Beke, dr. Emmylou Nelen, dr. Eric Van Tilborg, dr. Erik Schreurs, dr. Erika Flo, dr. Eva Cosyn, dr. Eva Decat, dr. Eva ter Haar, dr. Evelien Byloos, dr. Evelien Lenaerts, dr. Filip Roelens, dr. Fleur Helewout, dr. Franky D'Argent, dr. Frans Baccarne, dr. Frédéric Van Tongel, dr. Frederik Huysentruyt, dr. Geert Potloot, dr. Geert Van Moer, dr. Geoffry Lemeure, dr. Gerda Ottenbourg, dr. Gerda Vanderhaegen, dr. Godelieve Vaes, dr. Goele Nys, dr. Goele Smeets, dr. Griet Callens, dr. Griet De Cock, dr. Hanh Nguyen, dr. Hannah Govaert, dr. Hanne Beinsberger, dr. Hanne Vanhee, dr. Hanneke Vandenberghe, dr. Hannes Blockeel, dr. Hans Bogaert, dr. Hans Van den Abbeele, dr. Heidi Schaballie, dr. Heleen Debrabandere, dr. Herman Depoortere, dr. Hilde Tack, dr. Hilde Van Marcke, dr. Hilde Van Watermeulen, dr. Hilde Vandamme, dr. Ines Somers, dr. Inez Renders, dr. Inge De Gussem, dr. Inge Lampens, dr. Inge Matthijs, dr. Inge Vanlommel, dr. Ingeborg Van Eynde, dr. Jacob Merckx, dr. Jan De Lepeleire, dr. Jan Joris, dr. Jannaert, dr. Janssen, dr. Jasmine Leus, dr. Jasper Naert, dr. Jean Pierre Hoengenaert, dr. Jelle De Graeuwe, dr. Jeroen Stubbe, dr. Jessie De Ridder, dr. Jessie Errico, dr. Jo Borremans, dr. Jo Lisaerde, dr. Joachim Depaepe, dr. Johan Bourdeaud'huy, dr. Johan Van Acoleyen, dr. Johan Vliers, dr. Johan Wuyts, dr. Jonnaert, dr. Jos Truyen, dr. Julie De Meulemeester, dr. Julie Lefevere, dr. Justin Gouhie, dr. Kaatje Van Aerschot, dr. Karen Bertheloot, dr. Karen Sinnesael, dr. Karen Van Massehove, dr. Karen Van Roy, dr. Karin Decaestecker, dr. Karl Deleu, dr. Karl Logghe, dr. Karolien De Ceulaer, dr. Kathleen Hunninck, dr. Katja Clohse, dr. Katrien Butaye, dr. Katrien De

Schynkel, dr. Katrien Tilleman, dr. Katty Govers, dr. Kim Hermans, dr. Klaar Charlier, dr. Klaartje Antonissen, dr. Kris Van Haver, dr. Kristel Delanghe, dr. Kristel Van Tichelt, dr. Kristien Boel, dr. Kristien Kamoen, dr. Kristof Hillemans, dr. Laurent Mestdagh, dr. Leen Bouzen, dr. Leen Geyskens, dr. Leen Thienpont, dr. Lien Cruys, dr. Lien Lepère, dr. Lien Willems, dr. Lies De Sutter, dr. Lies Vanderperre, dr. Liesbet Vercammen, dr. Liesbeth Aeyels, dr. Liesbeth Christiaens, dr. Liesbeth Eggermont, dr. Liesbeth Schuermans, dr. Lieve Deruyter, dr. Linde Van Schelvergem, dr. Line Dalemans, dr. Lise Cornelis, dr. Lore De Greef, dr. Lore Vallaeys, dr. Lore Winters, dr. Lotte Maes, dr. Luc Debaere, dr. Luc Foucart, dr. Luc Pattyn, dr. Luc Seuntjens, dr. Lucas Ceulemans, dr. Lucia De Smet, dr. Lut Van Den Berghe, dr. Maes, dr. Maike Kuppens, dr. Marc Geeraert, dr. Marc Raes, dr. Maria Sophia Feytons, dr. Marie Coenen, dr. Marleen Devriese, dr. Marlien Buyssens, dr. Marlies Potoms, dr. Martien Humblet, dr. Martine Besouw, dr. Martine Debyser, dr. Meerschaut, dr. Michael Erkens, dr. Michel Creemers, dr. Michel Pôlet, dr. Mieke Bouvry, dr. Mieke Latruwe, dr. Mieke Martens, dr. Nele De Boer, dr. Nele Reynaert, dr. Nele Van Pee, dr. Nelly Aerts, dr. Nicky Huybrechts, dr. Nicola De Cono, dr. Norbert Van Mulders, dr. Olivia Vandeput, dr. Olivier Gernay, dr. Patrick Coursier, dr. Patrick Vanbelle, dr. Paul Lemay, dr. Peter Aerssens, dr. Peter De Sutter, dr. Philippe Alliet, dr. Philippe Gillis, dr. Piet Debackere, dr. Piet Van de Sype, dr. Piet Vanden Bussche, dr. Pieter Nevejan, dr. Pieter Op de Beeck, dr. Pieterjan Deraeve, dr. Quaegebeur, dr. Raaijmakers, dr. Rik Huybrechts, dr. Rita Stegen, dr. Rousseff, dr. Ruben Ryckeboer, dr. Sabine Fevery, dr. Sabine Van Baelen, dr. Sam Van Alphen, dr. Sanne Boonen, dr. Sandra Pollers, dr. Sara Lecoutere, dr. Sarah Haelewyn, dr. Sarah Maesen, dr. Saskia Wille, dr. Schamp, dr. Sofie Delameilleure, dr. Sofie Gadeyne, dr. Sophie Maes, dr. Staels, dr. Stefanie Matthé, dr. Stefanie Vermandere, dr. Stéphanie Biot, dr. Stephanie Bracke, dr. Stijn Allard, dr. Stijn Tiberghien, dr. Suzan De Wilde, dr. Swaegers, dr. Tania Claeys, dr. Thomas Eeckhout, dr. Tine Van Peer, dr. Tine Ysenbaert, dr. Tinneke Stals, dr. Tom Deputter, dr. Tom Lambrechts, dr. Tom Poelman, dr. Tom Seijnhaeve, dr. Valentin Degryse, dr. Van Hulle, dr. Vangheluwe, dr. Veerle Van Riet, dr. Vera De Vleesschauwer, dr. Wardenier, dr. Wendy Werckx, dr. Willem Van Nuffel, dr. Willieme, dr. Wouter De Rouck en dr. Wouter Van Mechelen, en hun collega's.

Last but not least, dank aan alle ouders en kinderen voor deelname aan de studie. Zonder uw goedkeuring, medewerking en prikjes in uw vinger was deze studie niet mogelijk geweest!

SERIOUS INFECTION IN ACUTELY ILL CHILDREN IN PRIMARY CARE

Validating clinical prediction rules and the added value of vital signs and point-of-care tests.

JAN VERBAKEL

May 2015

Acute infection is the most common presentation of children to ambulatory care. In contrast, serious infections are rare and often present at an early stage. Clinical prediction rules and point-of-care tests might aid early recognition of those serious infections and adequate referral to avoid complications or death. This is a dissertation presented by Jan Verbakel in partial fulfilment of the requirements for the degree of Doctor in Biomedical Sciences at the University of Leuven (KU Leuven), Belgium.

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